A CORRELATIVE STUDY OF RESPIRATORY FUNCTIONS AND ALLERGIC ASPECTS IN SPRAY PAINTERS

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In partial fulfillment for the award of the degree of

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BRANCH – V

Submitted by

Reg. No. 20112451

DEPARTMENT OF PHYSIOLOGY

GOVT. STANLEY MEDICAL COLLEGE

CHENNAI - 600 001

APRIL - 2015

CERTIFICATE

This is to certify that this dissertation entitled, **"A CORRELATIVE STUDY OF RESPIRATORY FUNCTIONS AND ALLERGIC ASPECTS IN SPRAY PAINTERS"** by the Post Graduate **Dr. S. U. CHITHRAPAVAI** for **M.D (PHYSIOLOGY) BRANCH - V** is a bonafide record of the research done by her during the period of study (2011 – 2015) in Govt. Stanley Medical College, Chennai- 600001.

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DECLARATION

I, **Dr.S.U.CHITHRAPAVAI**, solemnly declare that this dissertation entitled, **"A CORRELATIVE STUDY OF RESPIRATORY FUNCTIONS AND ALLERGIC ASPECTS IN SPRAY PAINTERS"** is a bonafide and genuine research work done by me at Govt. Stanley Medical College & Hospital during the period 2011 – 2015 under the guidance and supervision of **Dr.K.BALASUBRAMANIAN M.D.,** Professor and Head of Department, Department of Physiology, Govt. Stanley Medical College, Chennai – 600 001.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, towards partial fulfillment of the requirements for the award of **M.D. Degree (BRANCH – V) in Physiology.**

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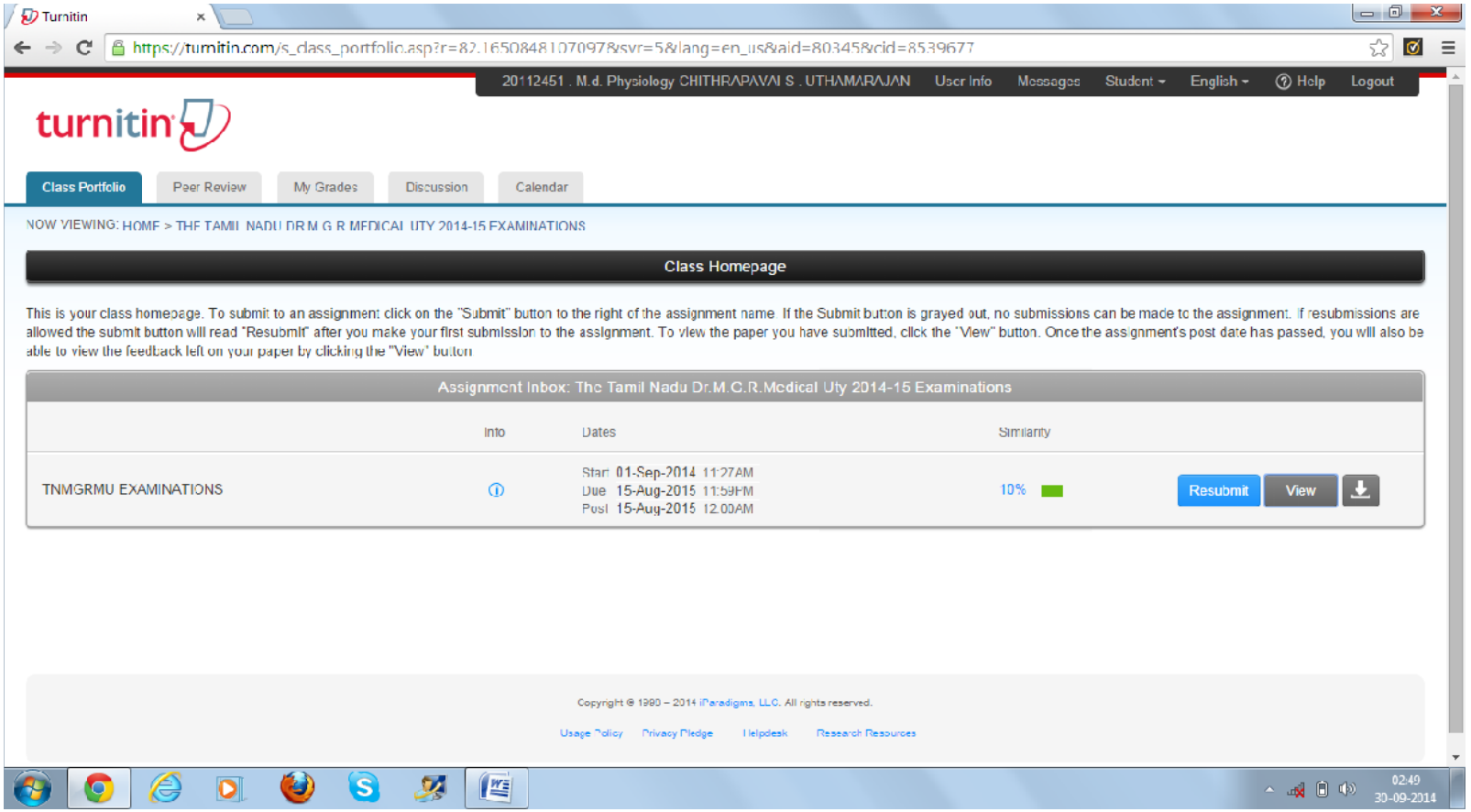
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ABBREVIATIONS

AEC	-	Absolute Eosinophil Count
ATS	-	American Thoracic Society
BHR	-	Bronchial Hyperrreactivity
CD	-	Cluster of Differentiation
Cm of H_2O	-	Centimetres of water.
CO_2	-	Carbon di Oxide
ELICA	-	Electro Chemi Luminescence Immunoassay
ELISA	-	Enzyme Linked Immunosorbent Assay
ERV	-	Expiratory Reserve Volume
FCM	-	Flow Cytometric Analysis
FEF 25-75% 25% and	-	Mean forced expiratory flow between 75% of FVC.
FEV_1	-	Forced Expiratory Volume in 1 second.
FRC	-	Functional Residual Capacity
FVC	-	Forced Vital Capacity
HDI	-	Hexamethylene Diisocyanate
HSA	-	Human Serum Albumin.
IC	-	Inspiratory Capacity
IgE	-	Immunoglobulin E
IgG	-	Immunoglobulin G
IRV	-	Inspiratory Reserve Volume
MDI	-	Methylene Diphenyl Diisocyanate
MMEF	-	Maximum Mid Expiratory Flow
MVV	-	Maximum Voluntary Ventilation
NCO	-	Isocyanate
O_2	-	Oxygen
OA	-	Occupational Asthma
OEL	-	Occupational Exposure Limits

OSHA	-	Occupational Safety and Health Administration
PACE	-	Prevention And Control Exchange
PEFR	-	Peak Expiratory Flow Rate.
PEL	-	Permissible Exposure Limits
PFT	-	Pulmonary Function Test
PPM	-	Parts per Million
PU	-	Polyurethane
RV	-	Residual Volume
SPSS	-	Statistical Package for Social Sciences
STEL	-	Short-Term Exposure Limits
SWORD	-	Surveillance of Work related and Occupational Respiratory Diseases
TDI	-	Toluene Diisocyanate
TLC	-	Total lung capacity
TV	-	Tidal Volume
TWA	-	Time-Weighted Average Concentration
VC	-	Vital Capacity

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ABSTRACT

A CORRELATIVE STUDY OF RESPIRATORY FUNCTIONS AND ALLERGIC ASPECTS IN SPRAY PAINTERS

Occupational environmental exposures play an important role in variety of health effects and the chief mode of entry is by inhalation as dust or fumes. Spray painters are continuously exposed to vapours, harmful substances and toxic materials during working hours. The harmful effects of dusts on the lungs depend on number of factors such as chemical composition, fineness, concentration of dust in air, period of exposure, concentration of exposure and health condition of the person exposed. Exposure to harmful substances in spray painting can have short term effects such as respiratory tract irritation, shortness of breath, influenza-like symptoms, tightness of chest, nausea, headache, dizziness and long term effects include cancer, sensitisation of the respiratory system, asthma, abnormal reduction in lung function, emphysema and central nervous system dysfunction. Toluene diisocyanate (TDI), diphenyl-methane diisocyanate (MDI), and hexamethylene diisocyanate (HDI) are the most frequently used diisocyanate monomers. Pulmonary function test (PFT) is a sensitive test to assess the effect of spray painting on lung functions. Determination of total IgE is useful as an aid in the diagnosis of allergic diseases. The electro chemi luminescence immunoassay ECLIA is intended for use on Elecsys and cobas e immunoassay analyzers. The Elecsys IgE II assay uses monoclonal antibodies specifically directed against human IgE. Aim of the study was to evaluate the changes in dynamic

respiratory functions of spray painters using Easyone Diagnostic Spirometer, to measure immunoglobulin E (IgE) level, to calculate absolute eosinophil count (AEC) and to compare parameters of study group to that of control group. Parameters studied were Forced Vital Capacity (FVC) (lit), Forced Expiratory Volume in 1st second (FEV_1) (%), FEV_1/FVC, Mean Forced Expiratory Flow ($FEF_{25-75\%}$) (lit/sec), Peak Expiratory Flow Rate (PEFR) (lit/min) and Maximum Voluntary Ventilation (MVV) (lit/min) followed by measuring level of IgE and Absolute Eosinophil Count. Spray painters of age group 25- 50 years, who are involved in spray painting for duration more than 2 years and controls not exposed to spray painting of age group 25- 50 years from Master health check- up clinic at Stanley Medical College are chosen for this study. After obtaining informed written consent from the subjects in their own language, pulmonary function test was recorded in research lab, Department of Physiology, Stanley Medical College using Easyone diagnostic spirometer. The entire procedure was explained and later demonstrated to the subjects satisfactorily. Interpretation of pulmonary function test parameters was done based on GOLD/ Hardie interpretation. After recording PFT, blood sample was collected from the subjects under strict sterile aseptic precautions. Data collected was stored and analyzed statistically by unpaired student t test using SPSS version 17.0. The data are expressed as Mean ± Standard deviation and P value < 0.05 is taken as significant. Of the total 30 subjects in study group, the mean age in years is 45 ± 4, mean height in centimetres is 158 ± 8, mean weight in kilograms is 73 ± 12 and mean BMI is 29 ± 4 and that of 30 subjects in control group the mean age in years is 44 ± 4, mean height in centimetres is

159 ± 6, mean weight in kilograms is 71 ± 10 and mean BMI is 28 ± 4. It was observed that there is a highly significant change in FVC (2.40 ± 0.31), FEV_1 (2.16 ± 0.26) and significant change in FEV_1/ FVC (0.90 ± 0.08) among study group when compared to that of control group FVC (3.29 ± 0.27), FEV_1 (3.11 ± 0.28) and FEV_1/ FVC (0.95 ± 0.04). There is a highly significant change in PEF (4.80 ± 1.74) and $MEF_{25-75\%}$ (3.01 ± 1.07) among study group when compared to that of control group PEF (6.46 ± 1.91) and $MEF_{25-75\%}$ (4.47 ± 0.82). There is a highly significant change in MVV (82.35 ± 20.07) among study group when compared to that of control group MVV (102.56 ± 25.15). IgE (410 ± 20) and AEC (333 ± 22) are significantly increased in study group when compared to that of control group IgE (97 ± 41) and AEC (228 ± 90). Duration of exposure to spray painting and pulmonary function test has been correlated and found that there is a statistically significant negative correlation existing between $MEF_{25-75\%}$ and duration of exposure to spray paint. No significant correlation demonstrated between FVC, FEV_1, FEV_1/ FVC, PEF, MVV, IgE levels and AEC and duration of spray paint exposure. While correlating IgE levels and AEC to that of parameters of pulmonary function test we found that the correlation was not statistically significant. FVC, FEV_1 and FEV_1/ FVC are better indicators to differentiate obstructive or restrictive lung disease. Isocyanate exposure in spray paint produce occupational asthma which causes an obstructive type of lung disease substantiated by normal or decrease in FVC, decrease in FEV_1 and decrease in FEV_1/ FVC ratio. In our study, there is significant decrease in FVC, FEV_1 and FEV_1/ FVC ratio. There is a significant decline in PEFR in study group when compared to control

group indicating a larger airway involvement due to spray paint. $FEF_{25-75\%}$ is a better indicator of smaller airway disease. We found that there is a statistically significant change in $FEF_{25-75\%}$ and there was a strong negative correlation between $FEF_{25-75\%}$ and duration of spray paint exposure indicating smaller airway involvement. MVV is more a sensitive indicator of airflow obstruction and in our study too shows a significant decrease in MVV when compared to control group emphasising the fact that obstructive airway disease is seen in isocyanate induced asthma. IgE levels were significantly elevated in our study group exposed to spray painting. AEC is significantly elevated in study group showing a strong relationship between isocyante exposure and allergic reactions. Correlation between duration of exposure to spray paint and IgE level and AEC in study group showed negative correlation, which was not significant statistically. This is due to the reason that the individual gets conditioned to the allergic aspect as the duration of spray paint exposure prolongs. We observe that measurement of pulmonary function test in individuals working in spray painting helps in early detection of any respiratory compromise and measuring IgE along with pulmonary function test serves as a sensitive indicator if done early during the period of exposure. Also measuring Absolute Eosinophil Count along with PFT and IgE serves as a strong evidence for allergic component involvement and bronchial hyperreactivity. In future, lung function test, IgE and AEC estimations may be a sensitive means to correlate isocyanate exposure and respiratory disease.

Key words: Spray painters, Occupational asthma, di-isocyanate, TDI, MDI, HDI, pulmonary function test, spirometry, Immunglobulin E, ECLIA, Flow cytometry, absolute eosinophil count.

INTRODUCTION

Occupational environmental exposures play an important role in many lung disorders. Exposure to air pollutants has a variety of health effects and the chief mode of entry of some of them is by inhalation as dust or fumes. Spray painters by virtue of their occupation are continuously exposed to vapours, harmful substances and toxic materials during working hours.

The harmful effects of dusts on the lungs depend on number of factors such as chemical composition, fineness, concentration of dust in air, period of exposure, concentration of exposure and health condition of the person exposed. Most of the workers do not wear any personal protective masks, goggles, aprons, hand gloves and filters to protect themselves.

Occupational health is defined as “Occupational health aiming at promotion and maintenance of the highest degree of physical, mental and social well being of workers in all occupations; the prevention among workers of departures from health caused by their working conditions; the protection of workers in their employment from risks resulting from factors adverse to health; the placing and maintenance of the worker in an occupational environment adapted to his physiological and psychological

equipment and to summarise the adaptation of work to man and of each man to his job" [1].

SPRAY PAINT

According to code of practice- spray painting, "Spray painting is a process by which air is driven across the mouth of a small outlet under such pressure as to draw the paint out and produce an air- paint mist from the jet of the spray-gun".

In addition, the paint may be fed under pressure to the gun. Spray painting may be carried out by hand or automatically. Airless spraying is a method by which pressure is applied directly to the paint, which is forced out of a nozzle.

Hazardous substances are "substances that the manufacturer (or importer) has determined are hazardous, in accordance with the National Occupational Health and Safety Commission's List of Designated Hazardous Substances or Approved Criteria for Classifying Hazardous Substances".

Normally, the substances can be identified as hazardous by their labels. Many substances encountered in spray painting are hazardous. They include paints, solvents, dusts, powders, lacquers, paint removers,

resins, adhesives, degreasers, surface preparation products, rust converters and rust removers [2].

Exposure to harmful substances used in spray painting can have serious health effects. Exposure can occur through different ‘routes of entry’ into the body. Routes of entry include inhalation, skin contact, ingestion, eye contact and injection through high pressure equipment. Depending on the substance, the severity of the harm could range from minor skin irritation to chronic lung disease.

Short term effects may include, respiratory tract irritation, shortness of breath, influenza-like symptoms, tightness of chest, nausea, headache and dizziness.

Long term effects may include cancer, sensitisation of the respiratory system, asthma, abnormal reduction in lung function, emphysema and central nervous system dysfunction.

Polyurethane (PUR and PU) is a polymer composed of a chain of organic units joined by carbamate (urethane) links. Polyurethane polymers are formed by reacting isocyanate with a polyol.

Di-isocyanates are bifunctional molecules used commercially to polymerise polyglycol and polyhydroxyl compounds to form polyurethanes.

Di-isocyanates are low-molecular-weight compounds characterized by highly reactive NCO groups and are one of the most commonly identified causes of occupational asthma [3,4,5].

Di-isocyanates are used as cross-linking agents in polyurethane products, such as foams, paints, lacquers, inks, insulating materials, varnishes, rubber modifiers, bonding and vulcanizing agents [6,7].

Toluene diisocyanate (TDI), diphenyl-methane diisocyanate (MDI), and hexamethylene diisocyanate (HDI) are the most frequently used diisocyanate monomers. Toluene di-isocyanate and diphenyl-methane di-isocyanate are generally less expensive and more reactive than other isocyanates. Toluene is a monomethyl derivative of benzene. It is used extensively as an industrial for paints and coatings, resins, oils and rubber.

The most common isocyanate monomer found in aliphatic polyurethane paint is hexamethylene di-isocyanate and is the ingredient which has generated the majority of concern.

The hexamethylene di-isocyanate is present in the uncured polyurethane paint coating and may be released during thermal decomposition of cured polyurethane paint coatings.

Spray painters exposed to hexamethylene di-isocyanate oligomer mixtures are among the occupational groups with the maximum incidence of occupational asthma in industrialized countries [8,9,10].

Besides allergic asthma, isocyanate exposure may also induce irritant asthma, hypersensitivity pneumonitis and possibly accelerated lung function decline. The polyurethane products continue to increase, along with the increase in number of workers who are at risk for exposure.

In the early years annual occupational asthma incidence was as high as 5 to 6%. The reduction of average toluene di-isocyanate concentrations below the 8-hour occupational exposure limit of 5 ppb (parts per billion) led to a decline in incidence of below 1%[11]. Conversely asthma symptom prevalence of up to 41% has been reported in toluene di-isocyanate users in less controlled environment and substitution of a different paint for one containing toluene di-isocyanate has halted an epidemic of asthma[12].

Inhaled di-isocyanates have reported to cause four different respiratory reactions.

1. Toxic bronchitis and asthma. Exposure to toluene di-isocyanate in an atmospheric concentration of 0.5 ppm (parts per million) causes irritation of mucosal surfaces, eyes, nose and throat [13].

2. Bronchial asthma caused by sensitisation to di- isocyanates.

3. Accelerated decline of Forced Expiratory Volume in 1 second (FEV_1).

4. Extrinsic allergic alveolitis, which has been reported particularly in workers exposed to diphenyl-methane di-isocyanate and hexamethylene di-isocyanate [14].

Of these four, bronchial asthma caused by hypersensitivity to isocyanates has been the most frequently reported and is probably the most important both in terms of prevalence and morbidity.

Agents that have been associated with induction of occupational asthma can be conveniently grouped into categories of high and low molecular weight compounds. All of these agents tend to sensitize the

individual, so that low ambient concentrations of the substance can ultimately cause significant bronchoconstriction.

PATHOPHYSIOLOGY OF ISOCYANATE INDUCED LUNG DISEASE

The harmfulness of an inhaled substance depends on its inherent toxicity, its ability to penetrate to the site at which it can exert its effects and the amount retained in the lung. Penetration depends on the ability of the particle to overcome the physical forces tending to bring it into contact with the walls of the airways namely sedimentation, impaction, interception, diffusion and electrostatic precipitation [15].

Sedimentation or movement under the influence of gravity proceeds at a rate that depends on the density and the square of the diameter of the particle; thus large dense particles fall rapidly and are deposited primarily in the nose, mouth and larger airways.

Impaction occurs when a particle fails to follow a change in direction of airflow and strikes the airway wall; it depends on the particle’s momentum so again large particles are filtered out by the larger airways.

Interception is a factor in the deposition of fibrous aerosols when the ends of long thin particles strike the airway wall.

Diffusion occurs as a result of Brownian motion, due to bombardment of very small particles by gas molecules in the air, and is particularly important with respect to deposition on alveolar walls of particles less than 0.5 µm. It is also the mechanism whereby inhaled toxic gases exert their effects on the airways and alveoli.

Electrostatic precipitation was until recently not thought to be important because of the conducting properties of mucus [16].

Another representation of lung deposition patterns shows that the highest rate of alveolar deposition occurs with a particle size around 0.02-0.06 µm (20-60 nm). This is the size range of particles in fume and nucleation mode of ambient air pollution[17].

Particles above 10 to 15 µm in diameter, because of their settling velocities in air, do not penetrate beyond the upper airways.

Particles below 10 µm in size are created by the burning of fossil fuels or high-temperature industrial processes resulting in condensation products from gases, fumes or vapours. These particles are divided into three size fractions on the basis of their size characteristics and sources.

Particles of approximately 2.5 to 10 µm (coarse-mode fraction) contain crustal elements such as silica, aluminium and iron. These particles mostly deposit relatively high in the tracheobronchial tree.

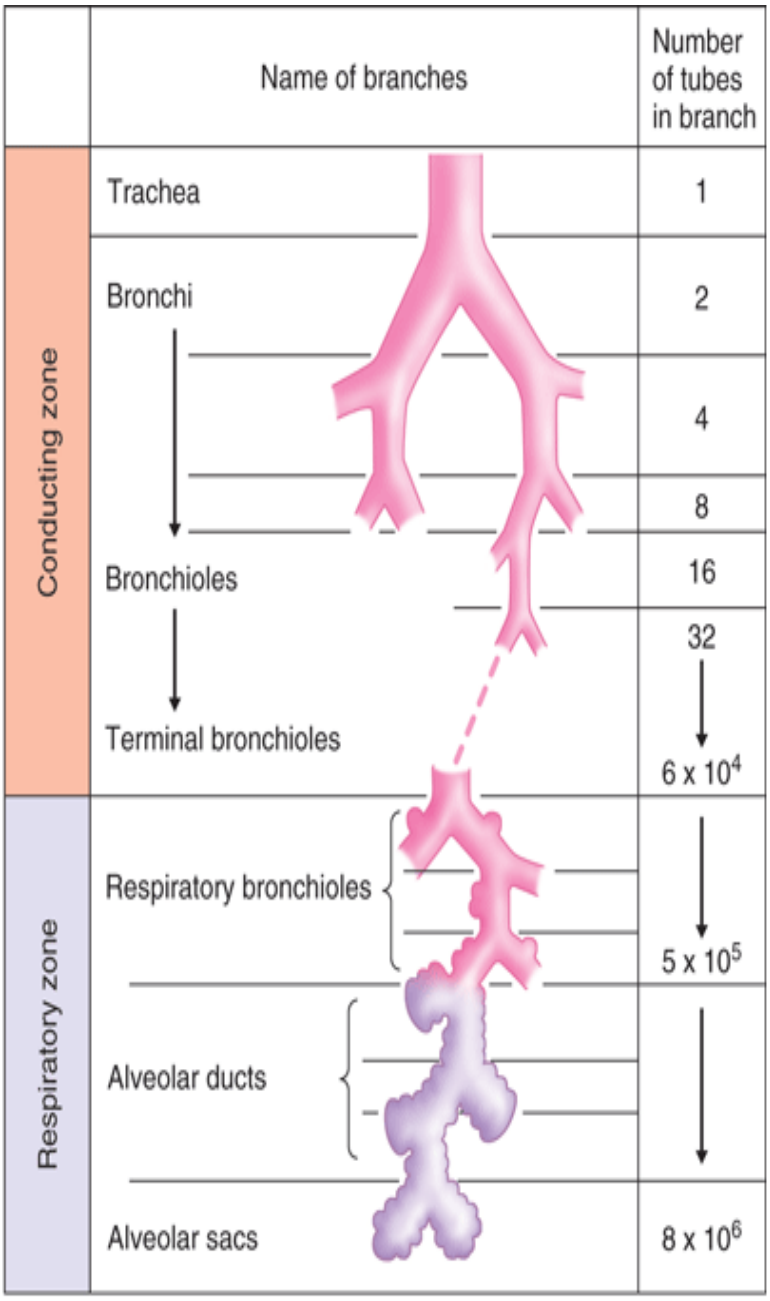
Particles smaller than 2.5 µm (fine-mode fraction or accumulation mode) are carried to the lower airways depending on the number of particles and the surface area on which potential toxic agents gets deposited.

The smallest particles, those less than 0.1 µm in size, (ultrafine fraction) make up the largest number of particles, which tend to remain in the airstream and deposit in the lung only on a random basis as they come into contact with the alveolar walls.

Once deposited in the respiratory tract the fate of the particle depends on the body's clearance mechanism and its ability to resist them. Larger particles deposited in the airways, are generally cleared efficiently within 24 hours by mucociliary mechanism[18,19]. Such cleared particles may be coughed up or swallowed. Particles reaching beyond the region of cilia and production of mucus are cleared much more slowly[20]. Deposition occurs predominantly at bifurcations of alveolar ducts[21]. The mechanism of particle removal involves ingestion by alveolar macrophages[22] or type I alveolar epithelial cells[23]. Having ingested a

particle the type I alveolar cell either delivers it into the interstitial space of the alveolar wall where it can be taken up by interstitial macrophages or flow with interstitial fluid into the lymphatics or dies and passes into the alveolar lumen[24].

PICTURE – 1 : STRUCTURE OF AIRWAY



The macrophage also seems to have several options: it may migrate up by the mucociliary escalator impelled by flow of alveolar surfactant and move to the terminal airways due to viscosity gradient[25]. Alternatively it can pass between the alveolar epithelial cells temporarily unlocking the epithelial junctions by proteolytic enzyme action, into the interstitial space. It may then proceed into the lymphatics to pulmonary and hilar nodes or pass back into the airways at the end of the terminal bronchiole, through lymphatic sumps [23].

The harm exerted by the particle once inhaled depends on its biological, chemical, physical properties and on amount inhaled. Biological factors include its ability to act as a sensitizer or to overcome attack by macrophages, provoke a primarily nasal reaction of a hypersensitivity type.

Chemical factors include the effects of gases or particle surfaces on cell or lysosomal membranes.

Physical factors apply when the particle is too large to be removed.

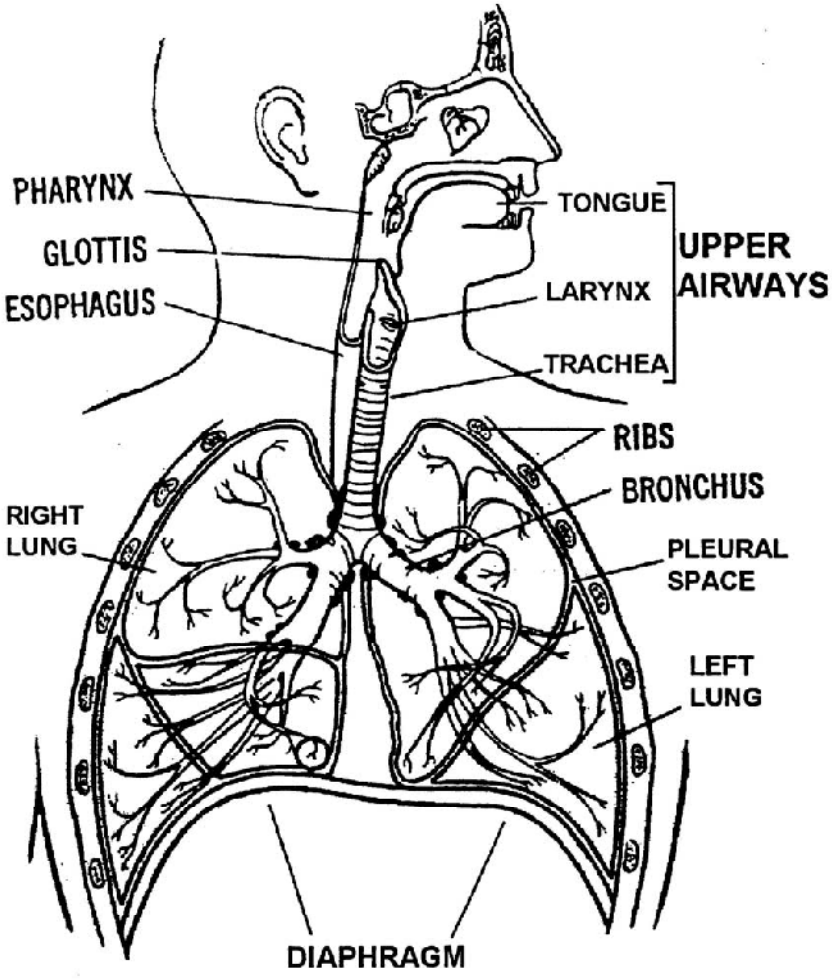
In addition, recent studies of micro fine particles of less than 50 nm diameter have shown paradoxical toxicity in rats at inhaled concentrations too low to cause pathological effects. The same

concentrations inhaled in larger micrometre- sized respirable particle do not produce any toxicity[26].

This strongly suggests that physicochemical factors associated with particle surfaces may be responsible for toxicity in particles associated with air pollution and fumes such as those derived from welding fumes and metal cutting[27].

Finally the total mass of dust inhaled is clearly important in that the lung's defences are evolved to enable removal of the modest amounts of particulate matter found in the ambient air and not the large amounts of inorganic matter that may be inhaled in the work place.

PICTURE – 2 : ANATOMY OF RESPIRATORY SYSTEM



American Lung Association: Occupational Lung Diseases: An Introduction. New York, NY. Macmillan. 1979: pp 10. (5).

PULMONARY FUNCTION TEST

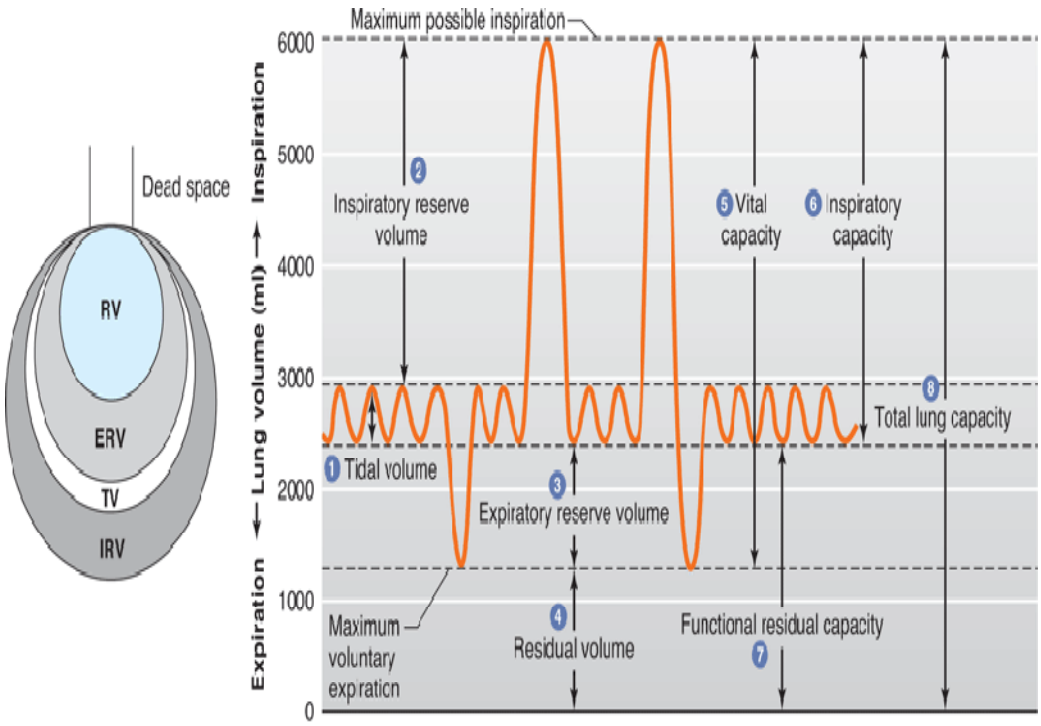
Aromatic di-isocyantes, on a constant exposure cause a decrease in respiratory functions which can be assessed by a simple tool called spirometry, which measures their pulmonary function. Serial measurements are useful in assessment of the type and extent of lung dysfunction, detection of early evidence of lung disease, longitudinal surveillance in occupational settings; follow up of response to therapy, determining the prognosis and disability evaluation[28].

Pulmonary function test (PFT) is a sensitive test to assess the effect of spray painting on lung functions. Clinical evaluation of lung function and the study of static lung mechanics begin with the measurement of lung volumes and the factors that determine these volumes. All lung volumes are subdivisions of total lung capacity.

Total Lung Capacity (TLC) is the total volume of air that can be contained in the lung. Lung volumes are reported in litres either as volumes or as capacities. A capacity is composed of two or more volumes. Four pulmonary volumes and four pulmonary capacities can be deduced. The lung volumes are,

1. Tidal volume: It is the volume of air inspired or expired with every breath and is approximately 500 ml in adult males.
2. Inspiratory reserve volume: It is the volume of air inspired maximally over end- inspiration. It is approximately 3.0 L.
3. Expiratory reserve volume: It is the volume of air that can be expired maximally from end- expiration. It is approximately 1.1 L.
4. Residual volume: It is the volume of air that remains in the lung after a forceful expiration. It is approximately 1.2 L.
5. Inspiratory capacity: It is the tidal volume plus inspiratory reserve volume.
6. Functional residual capacity: It is the residual volume plus expiratory reserve volume.
7. Vital capacity: It is the inspiratory reserve volume plus tidal volume plus expiratory reserve volume.
8. Total lung capacity: It is vital capacity plus residual volume.

PICTURE – 3 : RESPIRATORY VOLUMES AND CAPACITIES



Respiratory Volumes and Capacities for an Average Young Adult Male		
Measurement	Typical Value	Definition
Respiratory Volumes		
1 Tidal volume (TV)	500 ml	Amount of air inhaled or exhaled in one breath during relaxed, quiet breathing
2 Inspiratory reserve volume (IRV)	3000 ml	Amount of air in excess of tidal inspiration that can be inhaled with maximum effort
3 Expiratory reserve volume (ERV)	1200 ml	Amount of air in excess of tidal expiration that can be exhaled with maximum effort
4 Residual volume (RV)	1200 ml	Amount of air remaining in the lungs after maximum expiration; keeps alveoli inflated between breaths and mixes with fresh air on next inspiration
Respiratory Capacities		
5 Vital capacity (VC)	4700 ml	Amount of air that can be exhaled with maximum effort after maximum inspiration (ERV + TV + IRV); used to assess strength of thoracic muscles as well as pulmonary function
6 Inspiratory capacity (IC)	3500 ml	Maximum amount of air that can be inhaled after a normal tidal expiration (TV + IRV)
7 Functional residual capacity (FRC)	2400 ml	Amount of air remaining in the lungs after a normal tidal expiration (RV + ERV)
8 Total lung capacity (TLC)	5900 ml	Maximum amount of air the lungs can contain (RV + VC)

Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Pulmonary Function Tests including spirometry, lung volumes, and diffusing capacity are the most important tools to assess functional respiratory status in patients with occupational lung disease, as with non occupational diseases. PFT is important for evaluating dyspnea, differentiating obstructive from restrictive airway defects and assessing the degree of pulmonary impairment. Many lung volumes are measured with a spirometer, but neither the functional residual capacity nor the residual volume can be obtained by simple spirometry.

In clinical practice, while performing the pulmonary function test, along with the measurement of the various volumes and capacities, another parameter that is determined is forced expiratory volume (FEV).

Forced Expiratory Volume (FEV):

The volume of air that can be forcibly expired in the first second is called FEV_1 and the volume that can be expired in 2 second is called FEV_2 and the volume expired in 3 second is called FEV_3. Normally the entire vital capacity can be forcibly expired in 3 seconds. In normal individuals FEV_1/ FVC is approximately 0.8, which means that 80% of the vital capacity can be forcibly expired in the first second.

Forced Vital Capacity (FVC):

Most important dynamic lung volume which is measured clinically as an index of pulmonary function is forced vital capacity (FVC). FVC is the maximum amount of air that is forcefully breathed out after inflating the lung to the maximum by maximum inspiration.

FVC and FEV_1 are helpful in the diagnosis of lung disease. FEV_1/ FVC can be used to differentiate between various types of diseases. For instance, in obstructive lung disease like asthma both FEV_1 and FVC are decreased, but FEV_1 is decreased more than FVC. In fibrosis of lung, which is a restrictive lung disease, both FEV_1 and FVC are decreased, but FEV_1 is decreased less than FVC. Thus in fibrosis FEV_1/ FVC ratio actually increases[29,30].

Table 1: Interpretation of reports in Pulmonary Function Test:

Interpretation	**FEV_1**	**FVC**	**FEV_1/ FVC**
Normal person	normal	normal	normal
Airway obstruction	low	normal or low	low
Lung Restriction	low	low	normal
Combination of Obstruction/Restriction	low	low	Low

Adapted from Chronic Obstructive Pulmonary Disease, 5th Edition (1977). American Lung Association.

Table 2: Comparison of PFT report in obstructive and restrictive lung disease:

Interpretation	Obstructive Pattern	Restrictive Pattern
Normal	FEV_1/ FVC $\geq$ LLN	FVC $\geq$ LLN
Borderline	FEV_1/ FVC < LLN & $FEV_1 \geq$ LLN	-
Mild	FEV_1 < 100 & $\geq$ 70% Pred	FVC < LLN & $\geq$ 70% Pred
Moderate	FEV_1 < 70 $\geq$ 50% Pred	FVC < 70 & $\geq$ 50% Pred
Severe	$FEV_1 \leq$ 50% Pred	FVC $\leq$ 50% Pred

LLN- Lower Limit of Normal.

Adapted from American Thoracic Society : Lung function testing : Selection of reference values and interpretative strategies (1991). American Review of Respiratory Diseases 144 : 1202 – 1218.

FLOW- VOLUME LOOP

A newer way of measuring lung function clinically is the flow-volume curve or loop. A flow- volume curve or loop is created by

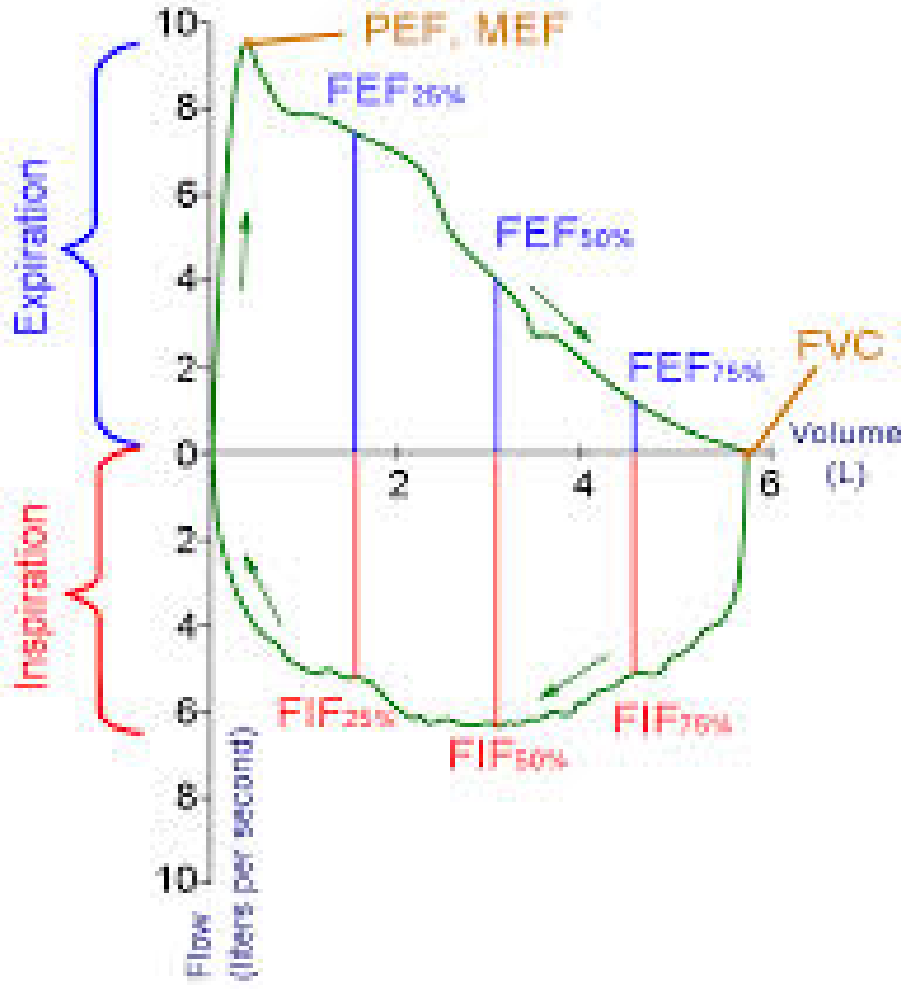
displaying the instantaneous flow rate during a forced maneuver as a function of the volume of gas. This instantaneous flow rate can be displayed both during exhalation (expiratory flow-volume curve) and during inspiration (inspiratory flow-volume curve). Expiratory flow rates are displayed above the horizontal line and inspiratory flow rates below the horizontal line. The flow-volume loop yields data for three main pulmonary function tests:

1. Forced Vital Capacity (FVC);

2. The greatest flow rate achieved during the expiratory maneuver, called the Peak Expiratory Flow Rate (PEFR), and

3. Expiratory flow rates. When the expiratory flow-volume curve is divided into quarters, the instantaneous flow rate at which 50% of the VC remains to be exhaled is called the FEF_{50} (also known as the $V_{max}50$), the instantaneous flow rate at which 75% of the VC has been exhaled is called the FEF_{75} ($V_{max}75$), and the instantaneous flow rate at which 25% of the VC has been exhaled is called the FEF_{25} ($V_{max}25$).

PICTURE – 4 : FLOW VOLUME LOOP



DETERMINANTS OF MAXIMAL FLOW

The shape of the flow-volume loop reveals important information about normal lung physiology that can be altered by disease. Inspection of the flow-volume loop reveals that the maximum inspiratory flow is the same or slightly greater than the maximum expiratory flow.

Two factors are responsible for the maximum inspiratory flow. First, the force that is generated by the inspiratory muscles decreases as lung volume increases above RV. Second, the recoil pressure of the lung increases as the lung volume increases above RV. This opposes the force generated by the inspiratory muscles and reduces maximum inspiratory flow. However, airway resistance decreases with increasing lung volume as the airway caliber increases.

The combination of inspiratory muscle force, recoil of the lung and changes in airway resistance causes maximal inspiratory flow to occur about halfway between TLC and RV.

During exhalation, maximal flow occurs early (in the first 20%) in the maneuver, and flow rates decrease progressively toward RV. Even with increasing effort, maximal flow decreases as RV is approached. This is known as "expiratory flow limitation" and can be demonstrated by

asking an individual to perform three forced expiratory maneuvers with increasing effort. As effort increases, peak expiratory flow increases. However, the flow rates at lower lung volumes converge; this indicates that with modest effort, maximal expiratory flow is achieved.

No amount of effort will increase the flow rates as lung volume decreases. For this reason, expiratory flow rates at lower lung volumes are said to be "effort independent" and "flow limited" because maximal flow is achieved with modest effort and no amount of additional effort can increase the flow rate beyond this limit. In contrast, events early in the expiratory maneuver are said to be "effort dependent"; that is, increasing effort generates increasing flow rates. In general, the first 20% of the flow in the expiratory flow-volume loop is effort dependent [31,32].

IMMUNOLOGICAL TESTING FOR LUNG DISEASE

The application of immunological tests in the investigation of occupational lung disease has widened because of development of reliable methods for identification of specific IgE antibody in serum. Specific IgE has also been identified in the sera of patients with asthma caused by some low molecular weight chemicals; particularly acid anhydrides [33] and reactive dyes [34].

Di-isocyanates, a low molecular weight compounds used by polyurethane workers, plastic, foundry and spray painters form an

isocyanate- protein complex. These agents also tend to cause IgE-dependent broncho constriction.

Specific IgE or IgG antibodies produced in these individuals are directed at the low molecular weight compound coupled to a protein within serum. There is also evidence that low molecular weight compounds induce asthma through IgE- independent mechanisms, possibly by affecting T lymphocytes directly as for isocyanates [35].

Immunoglobulins are the products of differentiated B cells and mediate the humoral arm of the immune response. The primary functions of antibodies are to bind specifically to antigen and bring about the inactivation or removal of the offending toxin, microbe, parasite, or other foreign substance from the body [36].

Determination of total IgE is useful as an aid in the diagnosis of allergic diseases. Immunoglobulin IgE plays an important role in immunological protection against parasitic infections and in allergy. Type I hypersensitivity is characterized by the occurrence of allergic reactions immediately following contact with an allergy initiating antigen (allergen). The binding of the allergen to sensitized mast cells or basophilic cells leads to cross linking of the IgE on the cell membrane and causes cell degranulation.

ECLIA (ELECTRO CHEMI LUMINESCENCE IMMUNOASSAY)

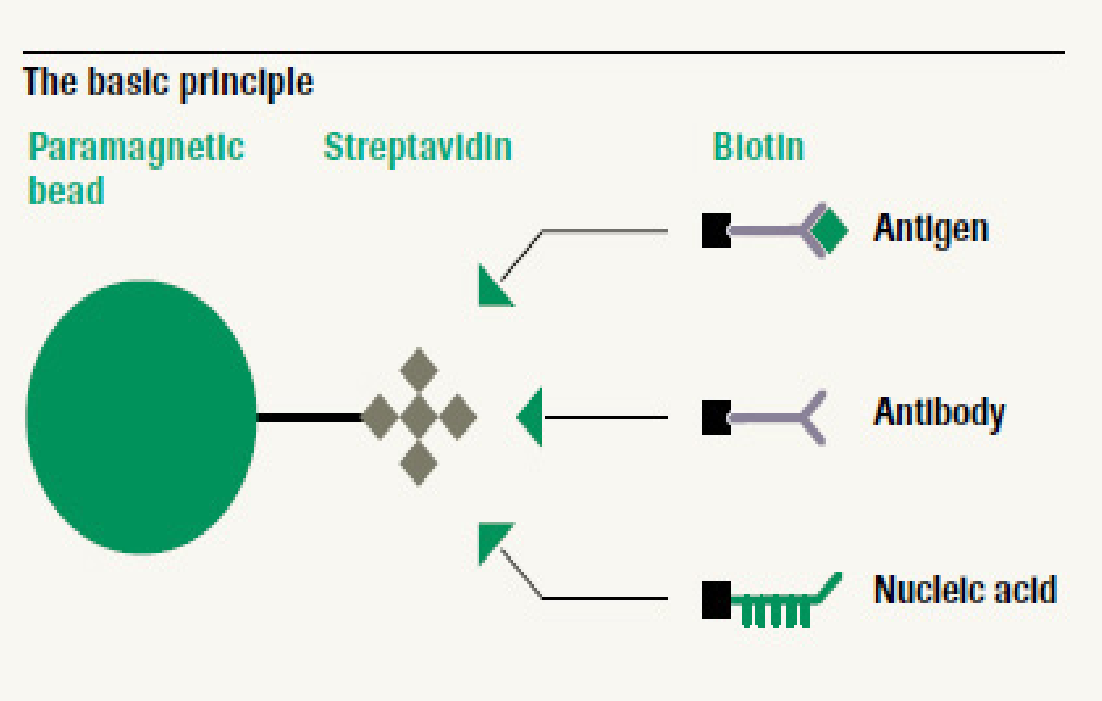
The electro chemi luminescence immunoassay ECLIA is intended for use on Elecsys and cobas e immunoassay analyzers. The Elecsys IgE II assay uses monoclonal antibodies specifically directed against human IgE.

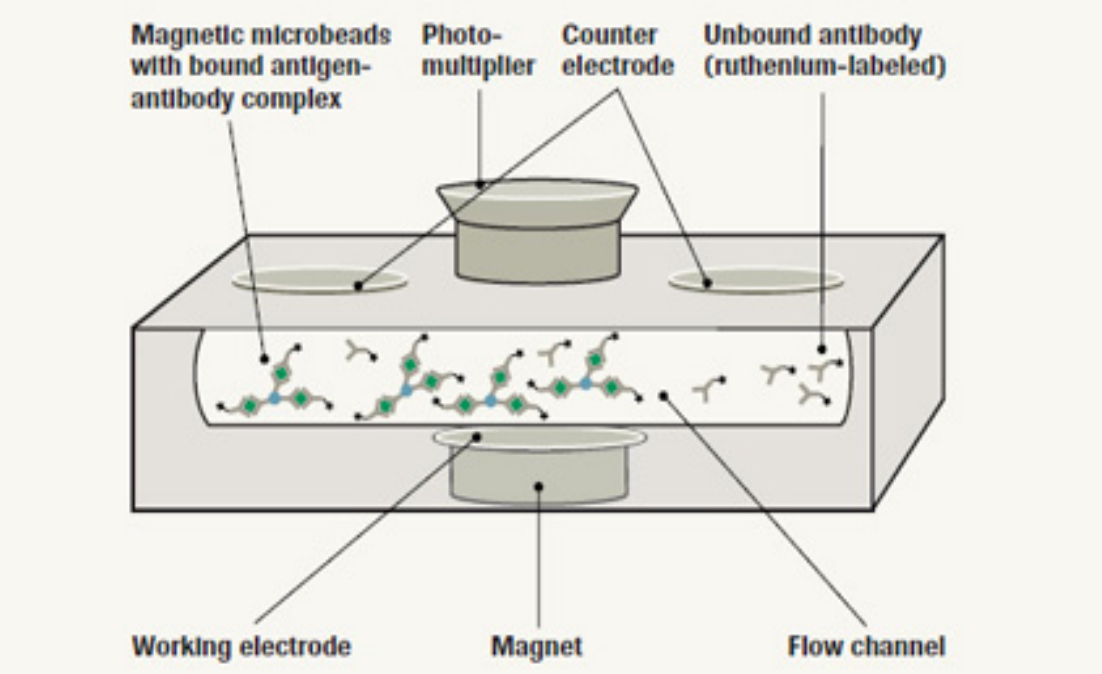
Immunoassay is for in vitro quantitative determination of immunoglobulin E in human serum and plasma. Test principle is sandwich principle and total duration of assay is 18 minutes.

1st incubation: IgE in the sample a biotinylated monoclonal IgE specific antibody and a monoclonal IgE specific antibody labelled with a ruthenium complex form a sandwich complex.

2nd incubation: After addition of streptavidin coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument- specifically generated by 2- point calibration and a master curve provided via the reagent barcode [37].

PICTURE – 5 : BASIC PRINCIPLE OF ECLIA





The IgE concentration in serum is normally very low (<0.001% of the total serum immunoglobulin). The IgE concentration is age dependent, with the lowest values being measured at birth. Its concentration gradually increases and becomes stabilised between the ages of 5- 7 years, although the IgE values vary greatly within particular age groups [38]. Recommended threshold values are [39,40,41]:

Table 3: Threshold values for IgE for different age groups:

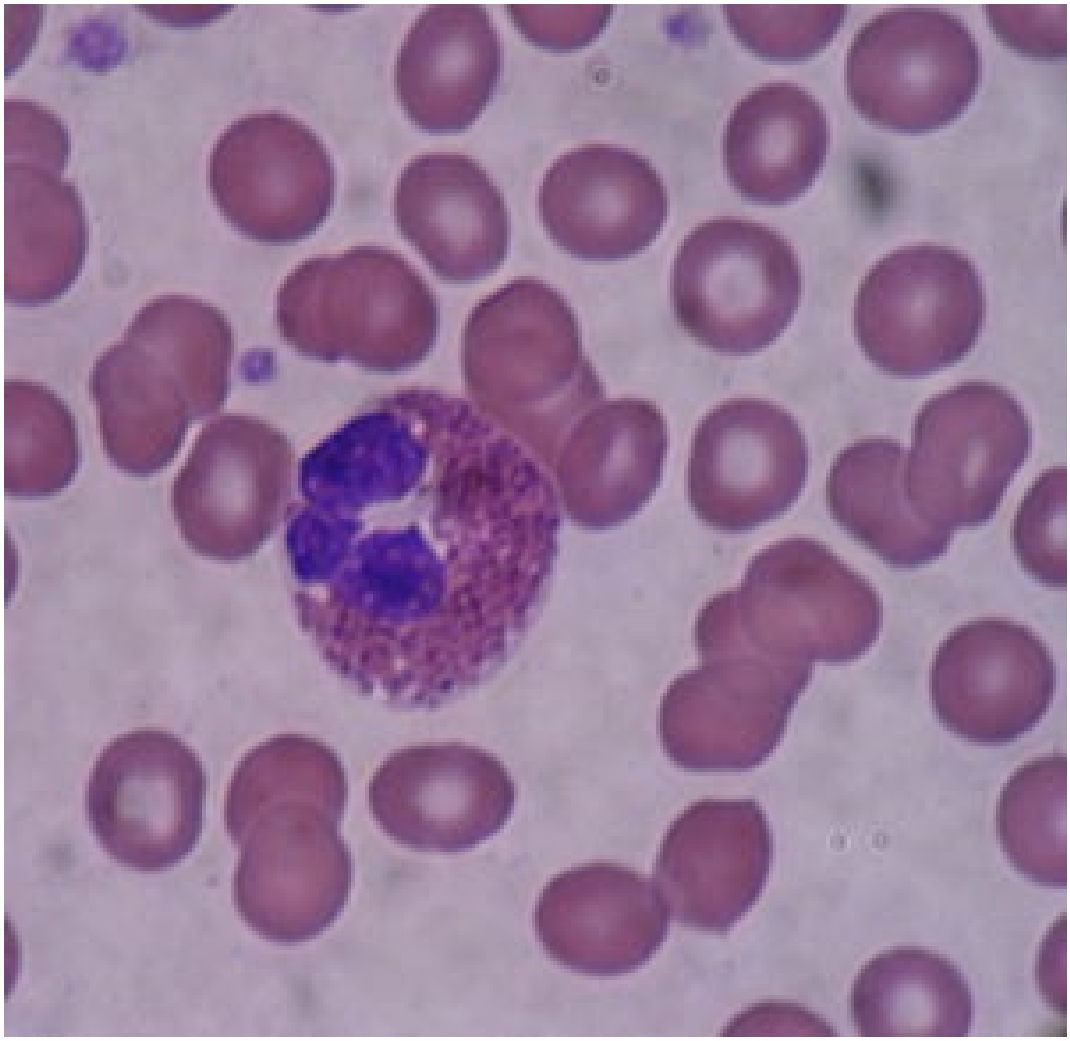
Age group	**IU/mL**	**ng/mL**
Neonates	1.5	3.6
Infants in 1st year of life	15	36
Children aged 1- 5 years	60	144
Children aged 6- 9 years	90	216
Children aged 10- 15 years	200	480
Adults	100	240

ABSOLUTE EOSINOPHIL COUNT

Cells of the eosinophilic series which normally make up about 3% of nucleated marrow cells mature in the bone marrow through stages similar to those of the granulocytic series. These have revealed a mean marrow transit time of 5.5 days, an intravascular compartment made up of a marginal pool and a circulating pool of equal size, and an intravascular half time of about 8 hours.

For each circulating eosinophil, 100 are reportedly present in the tissues where they are found primarily in the skin and in the submucosa of the respiratory, gastrointestinal and genitourinary tracts. The mature eosinophil contains a bilobed nucleus and distinctive large granules which stain orange- red using Wright’s stain.

PICTURE – 6 : EOSINOPHIL IN A SMEAR



The eosinophil is considered to be a homeostatic regulator of inflammation that attempts to suppress inflammatory tissue reactions and to prevent the excessive spread of inflammation. They proliferate in response to antigenic stimulation and contain substances that inactivate factors released by mast cells and basophils. The basophil surface membrane contains receptors for the Fc fragment of IgE molecules.

In acute allergic reactions a specific antigen reacts with IgE bound to basophils; and the basophils release their granule contents which include the allergic mediator, histamine. A related cell found in the tissues, the mast cell also possesses metachromatic granules containing histamine and surface membrane receptors for IgE.

Mast cells contain or can synthesise multiple mediators of immune and inflammatory responses; histamine, prostaglandins, leukotriens, platelet activating factor, proteases and other lysosomal enzymes and materials affecting chemotaxis of eosinophils and neutrophils. Through their activation and degranulation after the binding of antigen to IgE on the surface membrane, mast cells play a central role in triggering immediate hypersensitivity reactions. They also participate in inflammatory responses and tissue repair [42].

FCM (FLOW CYTOMETRIC ANALYSIS)

Flow cytometric analysis (FCM) has allowed detailed insights into the cellular biology of normal, reactive and neoplastic tissues. In its most general form, FCM would include any instrument that analyses a stream of individual cells from a cell suspension.

However, in current usage the term flow cytometer means an instrument that interrogates individual cells by light so as to determine intrinsic (light scatter/ cell size/ and granularity) and extrinsic (fluorescence/ antibody, and nucleic acid dye binding) characteristics of the cells. The flow cytometer is a sophisticated mixture of fluidics, optics, light detectors and computers.

The cell suspension is funnelled by the instrument into a single cell stream, which passes through the laser light. There is a characteristic scattering of the laser light by the cells that gives information of intrinsic cellular parameters. Some incident laser photons pass into the cytoplasm and are deflected by cytoplasmic granules or the cells [43].

REVIEW OF LITERATURE

REVIEW OF LITERATURE

OCCUPATIONAL ASTHMA

Occupational asthma (OA) is defined as, “asthma caused by or substantially made worse by agents inhaled in the occupational environment” [44].

Di-isocyanates have been the most commonly identified causing agent for OA in industrialized areas. Asthma among di-isocyanate exposed workers is due to a high level of irritant exposure at work or by sensitization to di-isocyanates. Alternatively, asthma may be coincidental or may be aggravated by work exposure [45].

Risk of occupational exposure to isocyanates is increasing substantially because of the rapidly expanding use of coating materials (paints), polyurethane foam manufacturing, and binders [46,47]. Spray paint contains isocyanate a low-molecular-weight compound.

Spray painting is a process by which exposure to isocyanates can be high. This spray paint creates fine mists or droplets of paint that may stay suspended in the air for a short period of time there by increasing the risk of inhalation, eye and skin exposure[48]. Some examples for di-

isocyanates are TDI (Toluene Di-Isocyanate), MDI (Methylene Diphenyl Di-isocyanate), and HDI (Hexamethylene Di-Isocyanate).

Compared with occupational asthma caused by other agents, those with occupational asthma due to di-isocyanates had a significantly earlier onset of asthma[49,50]. A follow-up study for 6 years was conducted in which the impairment correlated well with the frequency of high peak exposure to hexamethylene di-isocyanate. It was concluded in a study that occupational asthma is common disorder among automobile painters and duration of exposure has a significant effects on occupational asthma occurrence [51,52].

Exposure to di-isocyanate monomers has been assessed in various epidemiologic studies. In the majority of these studies mean or maximum exposure levels are reported for a population in which a measure of disease frequency is investigated [53- 59].

It is likely that humans have suffered from occupational asthma since the change from hunting to agriculture as a means of providing food. However the first recorded mention of breathlessness among handlers of grain was by Ramazzini in 1713, who is the father of occupational medicine [60].

The harmful effects of mining probably also date back to prehistory when humans first started to dig underground for flints to make arrowheads and axes and thus exposed themselves to quartz dust. Occupational exposure was also known to cause asthma occasionally [61].

PULMONARY FUNCTION TEST

Although Humphrey Davy had determined his own lung volume using hydrogen as the test gas in 1800, it was not until the 1840s that John Hutchinson laid the groundwork for modern pulmonary function testing: he devised a spirometer and used it to determine the subdivisions of the lung in a large number of healthy subjects, relating the measurements to height and age[62]. A spirometer used as early as 1846 by Hutchinson was a light bell- shaped container which is immersed in a water tank to form a seal. Modern modifications include dry spirometers made with bellows or a piston in a large cylinder. These often have an electrical output. As the bell moves up during exhalation the pen moves down marking the chart. In the tracing, the subject first breathed normally and the excursion of the pen gave the tidal volume[29]. Next he made a maximal inspiration followed by a maximal expiration. Normal breathing was then resumed.

Von Neergaard and Wirz, Rohrer developed and tested experimentally concepts involving pressures, flows and volumes. The full significance of Rohrer's work was not appreciated until the publications by Fenn and his group at the University of Rochester starting in the 1940s [63,64].

Fuchs and Valade in 1951 were the first to recognize that isocyanate exposure causes respiratory diseases and later on numerous studies have been carried out among paint works [65].

Wegman et al in 1977 reported on the chronic effects of toluene di-isocyanate, stated that there was a significant association between acute and chronic exposure to toluene di-isocyanate and decrement in FEV_1, and concluded that exposures to toluene di-isocyanate at 0.003 ppm or higher is unsafe [66].

Karol et al in 1982, studied in sensitized guinea pigs and sensitized worker and found a leading hypothesis concerning the pathogenesis of toluene di-isocyanate- OA, which is that toluene di-isocyanate acts as a hapten and undergoes nucleophilic addition reactions in vivo with airway proteins [67].

Chan –Yueng et al in 1986 reported that approximately 5 – 10 % of workers exposed to toluene di-isocyanate develop asthma and the asthmatic symptoms develop in weeks or months after the start of exposure. In sensitised individuals, exposures as low as < 0.005 ppm, may induce an attack of asthma[68]. They reported that sensitivity to toluene di-isocyanate can persist even for many years in the absence of occupational exposure and suggested that some patients with toluene di-isocyanate induced asthma do not recover from their disease even after being removed from isocyanate exposure. Moreover, continuous exposures to toluene di-isocyanate in sensitised patients led to further deterioration in lung function and increase in non-specific bronchial reactivity.

Banks et al in 1986 in his study discussed the adverse respiratory effects due to the isocyanates and reported that the respiratory impairment in association with exposure remains inadequate[69].

Rosenberg and Gamier in I986, described a technique of using a medical history questionnaire followed by the application of lung function tests in a follow-up study on isocyanate induced asthma cases. This study was multidimentional in nature and hence later a similar

approach was adopted by using a questionnaire followed by spirometric testing[70].

Mapp et al in 1988 showed that paint workers developed asthmatic reaction after exposure to isocyanate[71].

The Surveillance of Work related and Occupational Respiratory Diseases (SWORD) - a national scheme of UK was set up in 1989 by Professor Corbett McDonald. In 1989, 2101 cases of occupational lung disease were reported[72]. The overall annual incidence of occupational asthma during 1989 and 1990 was 22 per million working population [73]. The occupational sets with the highest incidence, was coach and spray painters with 658 rate 10^6/year.

Baur in his study about new aspects of isocyanate asthma done in 1990 in Germany found that when inhalation challenge test was done with isocyanates 14% of symptomatic persons were immunologically sensitized and concluded that at or above threshold limits there is a risk of deterioration in lung function even in asymptomatic workers[74].

A 6 year follow-up study by Torling et al in 1990 found that, compared to the smoking control subjects, the smoking spray painters had greater yearly reduction in FVC, FEV_1, and VC[75].

Berube et al in 1991 showed that changes in peak flow are proportionally less than the FEV, in the same individual with asthma [76].

Gannon et al in 1991 in a preliminary report of a surveillance scheme of occupational asthma in the West Midlands in the United Kingdom, found that the top four agents causing incidents of occupational asthma were isocyanates, colophony, flour and oil mist and these exposures closely matched the top four occupations spray painters, solderers, machine tool operators and bakers[77].

In June 1992 in South Africa, according to Government Notice 576, the Compensation Commissioner acknowledged the importance of isocyanate induced asthma and placed it on the second schedule of listed compensatable diseases[78].

In 1992 a sampling scheme was introduced and the annual incidence estimated at 3500[79].

Park et al in 1992 found that toluene di-isocyanate is the most common cause of OA in developing countries, with a prevalence of 2.9-13% in exposed workers. Burge in 1993 discusses the urgent need to have linear calibration of peak flow meters which may remove some of the confounding factors and concludes that methods are needed to increase

the sensitivity of serial peak flow measurements which should be achievable with the use of a computer diagnostic aid [80].

Vandenplas et al in 1993 found that every isocyanate should be considered hazardous regardless of its molecular form or volatility [3].

Swuste et al in 1994 presented a report in World Health Organization on hazard prevention and control in the workplace and launched the "**P**revention **and C**ontrol **E**xchange (**PACE**) Initiative with the following long term objectives:

- To promote awareness and political will concerning the need for prevention and control as a priority element of occupational health programmes, and
- To strengthen or develop, at the national level, technical and managerial capabilities for the utilization of successful approaches to the prevention and control of health hazards in the workplace, integrated into efficient and sustainable programmes, emphasizing anticipated preventive action, source control, safe work practices, workers' participation and environmental protection [81].

Randolph et al, in 1997, in his study about evaluating respiratory health status of automotive spray painters exposed to paints containing

hexamethylene Di-isocyanatesin the greater Durban area, found that even though decline in FEV_1 appear to be a suitable predictor of occupational asthma, in some cases it was found that the forced expiratory flow rate ($FEF_{25-75\%}$) was a more sensitive indicator of early changes in the small airways. This study concluded that PEFR measurements are inadequate to serve as an early warning indicator of possible occupational asthma. Moreover immunological tests showed no correlation with declines in FEV_1. This study demonstrates the difficulties in correlating immunological status with clinical and lung function findings in workers exposed to hexamethylene di-isocyanate, as a means of predicting occupational asthma. Randolph et al recommended routine spirometric lung function testing of all spray painters, the use of high volume- low pressure spray guns and the wearing of positive pressure airline masks, regular monitoring of spray booths, measurement of hexamethylene di-isocyanate concentrations, airflow velocities and airflow patterns within the booth and implementation and enforcement of stricter control measures [82].

Ogden and Topping in 1997 defined the occupational exposure limits (OEL) for airborne chemicals in Britain and concluded that exposures below the OELs do not mean that all workers are protected [83].

Vincent in 1998, stated that Occupational Exposure Limits (OELs) are a key element in risk management and are often incorporated in legal standards[84]. Although obvious exposure to known harmful agents should be controlled regardless of any existing regulation, establishment of a control limit often draws attention to a substance. Occupational exposure limits are usually expressed in one of the following forms:

- Time-weighted average concentration (TWA), which is the average concentration over a full shift, usually 8 hours.
- Ceiling concentration, which is an instantaneous concentration (in so far as this can be measured) not to be exceeded at any time.
- Short-term exposure limits (STEL), which is the average concentration over a specified time, e.g. 15 minutes [85].

Asthma which accounted for 28% of cases was the single most common diagnostic category. Isocyantes have consistently been the most commonly reported cause accounting for 20% of cases. In Britain at present isocyanates seem to be the most common cause of occupational asthma and isocyanate asthma continues to provide a typical example of asthma attributable to occupational chemicals[86]. The results have been conflicting and have stimulated much controversy. A major multicentre surveillance programme in Britain revealed no hint of a copd effect, while

study of a single isocyanate producing plant in the USA suggested a crippling occupationally induced mean decline in FEV_1 exceeding 100ml/year [87,88].

Diem and colleagues conducted a 5 year investigation of workers in a new toluene diisocyanate manufacturing plant included an extensive series of isocyanate exposure measurements, from which the workforce was usefully separated into categories of low –average cumulative exposure and high – cumulative exposure [89]. The high exposure group did show a significantly greater annual decline in FEV_1 than the non-smokers of low exposure group. Thus the investigation suggested a modest excessive decline in FEV_1 as a consequence of either isocyanate exposure or smoking, without there being any additive or multiplicative effects.

One study reported persistent respiratory symptoms in 83 percent of workers who have been away from isocyanate exposure for 4 years. Another study demonstrated that 7 of 12 subjects with toluene di-isocyanate- induced asthma continued to have non- specific airway hyperreactivity 2 years after removal from the work environment [90]. Exposures to a number of organic dusts or chemical agents capable of producing occupational asthma result in pronounced obstructive patterns

of pulmonary dysfunction that may be reversible. Measurement of change in forced expiratory volume (FEV_1) before and after a working shift can be used to detect an acute inflammatory or bronchoconstrictive response. An acute decrement of FEV_1 over the first work shift of the week is a characteristic feature of exposure to spray paint among workers.

Peters et al in 1975, Mapp et al in 2001 and Park et al in 2002, in different studies proved that three di-isocyanates cause occupational asthma (OA): toluene diisocyanate (TDI), 4, 4-diphenylmethane diisocyanate (MDI), and 1,6-hexamethylene diisocyanate (HDI) [91- 93].

Becklake et al in 2006 proved that BHR is closely related to variable airway obstruction and is usually considered a hallmark of asthma in epidemiological studies. Specific IgE was found in only one of the 19 workers with both BHR and asthma-like symptoms and in none of the nine workers with both BHR and an FEV_1/ FVC ratio of 70% [94].

Ye YM et al in 2006 concluded that the pathogenic mechanisms of isocyanate induced asthma remain incompletely understood and no reliable method of serological testing has been established [95].

Pronk, Raulf-Heimsoth et al in 2007, concluded that asthma-like and COPD-like symptoms are associated with isocyanate exposure level

in workers exposed to mainly hexamethylene di-isocyanate oligomers in the spray paint. Pronk found that exposure to isocyanates is associated with bronchial hyperresponsiveness (BHR) which is the hallmark of asthma. The FEV_1/ FVC ratio and several flow parameters were significantly lower in spray painters compared with other workers. In this study, a clear and positive association was found between exposure to isocyanate oligomers and BHR [96].

Similar findings were revealed by Ould-Kadi et al in 2007, who found lowered FEV_1 in solvent exposed group of workers than the control group [97].

Chattopadhyay et al in 2007, in 2.5 years follow-up study observed that pulmonary function parameters of isocyanate exposed workers for long duration were reduced even in very low concentration car painting and automobile painting workers [98].

Nmai et al in 2011, in his article summarized that a potential biomarkers is essential for isocyanate induced asthma, based on different mechanisms, including immunologic, genetic neurogenic and protein markers and concluded that the detection of serum specific IgE or IgG is helpful even though this alone is not sensitive enough to serve as a bio marker. However it is certainly useful for confirming isocyanate specific

type I hypersensitivity, documenting exposure and monitoring subclinical conditions [99].

In guidelines for controlling health hazards in painting operations in 2012 US Army Public Health Command Technical Guide, suggested that in sufficient concentrations, hexamethylene di-isocyanate may cause acute pulmonary symptoms to include cough, shortness of breath, pain on respiration, increased sputum production, and chest tightness. In a small percentage of the workforce, it may produce asthmatic symptoms through an allergic, immunoglobulin E-mediated mechanism. Sensitive individuals may exhibit a decrease in forced expiratory volume in 1 second (FEV_1) on pulmonary function testing after being exposed during the work shift, as compared to pre shift values. A longitudinal study of workers exposed to toluene diisocyanate, suggests that low level for chronic exposures may result in an increased decrement in pulmonary function [100].

Metwally et al in 2012 [101] and Zailina et al in 2013 [102] in different studies assessed pulmonary function of paint industry workers.

Bishara et al in 2013, studied effect of flour mill dust on pulmonary function and effect of duration of exposure and found a significant

change in FVC and FEV_1 and no significant change as duration of exposure increases [103].

Mandal et al in 2013, while assessing the pulmonary function of paint industry workers from west Bengal found that there is significant correlation between pulmonary functions and duration of exposure to solvents and dust and found that most paint workers have restrictive pulmonary function impairment [104].

IMMUNOGLOBULIN E (IgE)

There are studies suggesting that isocyanates may interact directly with elements that modulate inflammation. Because these compounds are very reactive they may affect membrane receptors or enzymes involved in inflammatory pathways. One study has demonstrated specific IgE and IgG antibodies to isocyanates coupled to human serum albumin in sera of individuals with symptoms and positive inhalation challenge test with isocyanates [90].

Johansson et al in 1968 and Barbee et al in 1981, found that nearly 50% of the allergic subjects have the total IgE concentrations that are two standard deviations above the mean of a normal control group [105,106].

In a study by Pezzini in 1984, they found a specific IgE-mediated response was evaluated in twenty-eight workers exposed to toluene di-isocyanate or diphenyl-methane di-isocyanate. The results suggest an association between the presence of specific IgE, early asthmatic symptoms and heavy episodic exposure [107].

Patterson et al in 1987 found that isocyanate induced asthma is IgE mediated, but presence of a specific diisocyanate IgE has been shown only in a few workers with symptoms [108].

Musk, Peters and Wegman in 1988 stated that specific IgE antibodies to isocyanates have been reported but specific IgE to diisocyanate conjugates have not been identified[109].

At the same time Grammer et al in 1988 reported on a study of 150 spray painters' measurements of ambient isocyanate levels and measurements of serum antibody to hexamethylene di-isocyanate bound to human serum albumin were evaluated [57].

Roy Patterson et al in 1990 studied immunoassay for three isocyanates, and found high levels of IgG and IgE antibodies for hexamethylene di-isocyanate - HSA and toluene di-isocyanate -HSA in a 34 year old individual who presented with hemoptysis, dyspnea and

bilateral opacities which progressed to respiratory failure. He proposed that the pathogenesis of this case of hemorrhagic pneumonitis is immunologic because of uncontrolled exposure to hexamethylene di-isocyanate and toluene di-isocyanate [110].

Agha et al in 1997 proved in their study that among all age groups, difference between mean IgE levels between allergic subjects and controls was significant [111].

Rosemary et al in 1998 investigated the utility of specific IgE measurement in the diagnosis of isocyanate- induced asthma. 58 of 101 patients referred for investigation were diagnosed as having isocyanate-induced occupational asthma by means of history, serial peak flow records, and bronchial provocation tests. Specific IgE antibodies to toluene diisocyanate: human serum albumin (HSA), diphenylmethane diisocyanate: HSA, and hexamethylene diisocyanate: HSA were measured in all patients by Phadebas RAST. Specific IgE to isocyanates is a more specific than sensitive index of occupational asthma and concluded that with a RAST score of 3 or more, it is wholly specific and therefore diagnostic of isocyanate-induced asthma [112].

Several groups including Baur et al in 1984, Tee et al in 1998, Son M et al in 1998, have detected serum specific IgE antibodies to toluene

di-isocyanate - HSA conjugate in the sera of workers with a positive bronchial challenge to toluene di-isocyanate [113- 115].

Tee et al reported that sensitivity of serum specific IgE to isocyanate was the highest when blood was taken less than 30 days after the last exposure. However, serum specific IgG to isocyanate may persist for several years after the last exposure to toluene di-isocyanate.

Andre et al in 2005, in twenty-nine subjects demonstrated increased levels of specific IgE and/or IgG antibodies to isocyanates. Although increased levels of specific IgE and/or IgG antibodies have been documented in individual cases of occupational asthma caused by isocyanates, the frequency among workers with occupational asthma is still unknown. He concluded that the levels of specific IgG to isocyanates (hexamethylene di-isocyanate and diphenyl-methane di-isocyanate) bear a satisfactory association, in terms of sensitivity and specificity, suggesting that an immunologic mechanism is involved [116].

Park HS, Kim HY et al in 2001, Park HS et al in 2002 and Ye YM et al in 2006 in different studies found that serum specific IgE and IgG antibodies to toluene di-isocyanate human serum albumin conjugate were found to have diagnostic value [117- 119].

Raulf et al in 1998 and Wisnewski et al in 2006 in different studies found that other mechanisms, like cell mediated allergic reactions or pulmonary irritation are likely to be involved [120,6].

Anjoeka et al in 2007, studied exposure- response relationships of respiratory symptoms and sensitization in population occupationally exposed to isocyanate oligomers during spray painting. Specific IgE and IgG to hexamethylene diisocyanate (hexamethylene di-isocyanate) were assessed in serum by Immuno CAP assay and enzyme immunoassays. Respiratory symptoms were more prevalent in exposed workers than among comparison office workers. Log–linear exposure–response associations were found for asthma like symptoms, chronic obstructive pulmonary disease–like symptoms, and work-related chest tightness. The prevalence of specific IgE sensitization was low, but IgE to oligomeric hexamethylene di-isocyanate – HSA was associated with exposure and work related chest tightness. The prevalence of specific IgG was higher and strongly associated with exposure [96].

Aurelia et al in 2007 concluded that allergic sensitization mediated by IgE is the basis of allergic diseases and elevated total IgE proved to be a diagnostic criterion for allergic diseases inspite of well-known limitations [121].

Lushniak et al in 1998, Aul DJ et al in 1999 and Hur GY et al in 2008 have measured diphenyl-methane di-isocyanate - specific antibodies by using enzyme linked immunosorbent assay (ELISA) [122- 124].

Jagadeeshwar et al in 2012 found in their study that a total serum IgE level was considered to be higher in allergic subjects than in healthy subjects [125].

ABSOLUTE EOSINOPHIL COUNT

Eosinophilia is commonly encountered during routine investigation. However in the modern literature, only little work has been done in the field of blood eosinophilia.

Wykoff et al in 1986 found that in developed countries that the most common etiology for eosinophilia is seasonal and perennial rhinitis, hay fever, asthma and allergic drug reaction [126].

Enright et al in 1989 concluded that most asthmatics, especially those with intrinsic asthma have eosinophilia [127].

Brigden et al in 1997 and Kobayashi et al concluded that allergy and atopy is described as the leading cause for eosinophilia in developed countries [128,129].

Leukens et al in 1972, Wardlaw et al in 1990 and Rothenberg et al in 1998, proposed different values of eosinophilia [130- 132].

Marc.E.Rothenberg in 1998 classified eosinophilia into

Mild: 351-1500/mm3 of blood.

Moderate: 1500-5000/mm3 of blood.

Severe: >5000/mm3 of blood.

Bousquet et al in 2001 in a cross-sectional study showed that allergic rhinitis is strongly associated with asthma and BHR [133].

“A Study of Clinical Profile and Spontaneous Course of Eosinophilia” by Anshu et al in 2002 found in their study that most of the eosinophilic patients were symptomatic [134].

Usually patients of eosinophilia are asymptomatic as reported by Schulte et al in 2002 [135].

As said by Xu et al in 1997 and Brutsche et al in 2006 bronchial hyper reactivity is a risk factor for development of bronchial asthma [136,137].

In a study by Ajithkumar et al in 2013 study was done to find out the correlation and predictive value of absolute eosinophil count for bronchial hyperreactivity and revealed a relationship between peripheral blood eosinophilia and bronchial hyperreactivity in allergic rhinitis and a strong association between allergic rhinitis and lower airway dysfunction[138].

PHYSIOLOGY OF RESPIRATION

Respiratory system comprises of lung, airways, muscles of thorax and abdomen, the integrated action of which is controlled by the respiratory centre in the central nervous system according to inputs from the receptors which monitor the various parameters related to the function. Lungs are the principle organs of respiratory system.

Physiological anatomy

Upper airways:

Nose, sinuses, pharynx and larynx constitute the upper airways. Inspired air is humidified and conditioned by upper airways so that when it reaches lung it will be at body temperature. It helps to filter particles with size more than 10 micron in the inspired air. Respiratory epithelium of upper airways secretes immunoglobulin, inflammatory mediators,

interferons, which helps in host defence. Sinuses resonates the voice and lightens skull. Larynx is situated at the upper part of trachea and helps in sound production.

Conducting airways:

Conducting airway starts at trachea and include first 16 generations, which includes bronchi, bronchioles and terminal bronchioles. Trachea divides into two main bronchi which in turn divide in a dichotomous or asymmetric pattern. This arrangement increases cross sectional area from 2.5 cm^2 in trachea to 11800 cm^2 in alveoli. Hence the velocity of airflow decreases in small airways [139]. Conducting airways act as a conduit for airflow. It helps in body defence. Non ciliated cuboidal epithelial cells called Clara cells secrete defence markers like secretory immunoglobulin, collectins, defensins, peptidases, proteases, reactive oxygen and nitrogen species.

Alveolar airways:

Alveolar airway constitutes last 7 generations including respiratory bronchioles, alveolar ducts, and alveoli. The total area of the alveolar walls in contact with the capillaries in both lungs is about 70 m^2. Alveoli

are surrounded by pulmonary capillaries. Alveoli are lined by two types of cells; type I and II pneumocytes. Type II cells secrete surfactant.

Thoracic cage:

The ancients wondered about how air moved into and out of the lungs and as far back as Erasistratus the diaphragm was recognised to be involved in breathing.

Galen was aware that the lungs fill the chest cavity, they are moved by the actions of the thorax and the large airways enlarge and lengthen during inspiration. Mayow, one of the oxford physiologists, drew heavily on the work of colleagues, such as Boyle and Hooke, to develop considerable insight into the mechanics of breathing. He also built the first model on record of the chest as a bellows, which contained a bladder within it [63].

During the decade between 1915 and 1926, Rohrer and his colleagues provided a remarkably comprehensive synthesis of respiratory mechanics that included a description of the static pressure - volume characteristics of the respiratory system, the work of breathing. Interpretation of pulmonary function test requires an insight about the respiratory muscles and work of breathing.

The major muscles of respiration include the diaphragm, the external intercostals and the scalene which are all skeletal muscles. Skeletal muscles provide the driving force for ventilation; the force of contraction increases when they are stretched and decreases when they shorten. The force of contraction of respiratory muscles increases at larger lung volumes.

The process of respiration or gas exchange begins with the act of inspiration, which is initiated by contraction of the diaphragm. The diaphragm is the major muscle of respiration and it divides the thoracic cavity from the abdominal cavity. On contraction, the diaphragm protrudes into the abdominal cavity and moves the abdomen outward to create negative pressure inside the chest. This increases the vertical dimension of the chest cavity and creates a pressure difference between the thorax and abdomen.

During quiet breathing the diaphragm moves approximately 1 cm; however, during deep-breathing manoeuvres (vital capacity), the diaphragm can move as much as 10 cm. The diaphragm is innervated by the right and left phrenic nerves, which have their origins at the third to fifth cervical segments of the spinal cord.

The other important muscles of inspiration are the external intercostal muscles, which pull the ribs upward and forward during inspiration. This causes an increase in both the lateral and antero posterior diameter of the thorax.

Innervation of the external intercostal muscles originates from intercostal nerves that arise from the same level of the spinal cord. Paralysis of these muscles has no significant effect on respiration because respiration is primarily dependent on the diaphragm.

Accessory muscles of inspiration are the scalene muscles, which elevate the sternocleido mastoid and the alae nasi, which cause nasal flaring. However, they do contract vigorously during exercise, and when airway obstruction is significant, they actively pull up on the rib cage. During normal breathing they anchor the sternum and upper ribs.

Because the upper airway must remain patent during inspiration, the pharyngeal wall muscles (genioglossus and arytenoid) are also considered to be muscles of inspiration. All of the rib cage muscles are voluntary muscles that are supplied by intercostal arteries and veins and innervated by motor and sensory intercostal nerves.

Exhalation during normal breathing is passive, but it becomes active during exercise and hyperventilation. The most important muscles of exhalation are those of the abdominal wall (rectus abdominis, internal and external oblique, and transversus abdominis) and the internal intercostal muscles, which oppose the external intercostal muscles (i.e., they pull the ribs downward and inward). The inspiratory muscles do the work of breathing.

During normal breathing, work is low and the inspiratory muscles have significant reserve. Respiratory muscles can be trained to do more work, but there is a finite limit to the work that they can perform [32].

PULMONARY FUNCTION TEST

PFT are done to assess ventilation, diffusion, perfusion, and mechanics of respiration. The components of PFT include spirometry, measuring diffusing capacity and measurement of RV and TLC. Spirometry is the most important tool for assessing the functional status of the respiratory system. PFT helps in evaluation of dyspnoea, to differentiate obstructive and restrictive lung disease and in assessing degree of pulmonary impairment.

Indications of PFT:

1. To investigate patients with suspected pulmonary disease.
2. For assessing progress and response to treatment in patients with asthma, fibrosis and pulmonary vascular diseases.
3. For pre operative evaluation before lung resection, abdominal and cardio thoracic surgeries.
4. Evaluation of patients having risk of developing lung diseases like, exposure to radiation, medications, environmental and occupational hazards.
5. Surveillance following lung transplantation to rule out rejection, infection and obliterative bronchiolitis [140].

Indications of spirometry:

Spirometry is a part of PFT, used to assess the ventilatory function of the lung. It's a simple non invasive and easy to perform test, but requires substantial participation from the individual.

Diagnostic:

1. To measure the effects of disease on pulmonary function.
2. To screen individuals at risk of having pulmonary disease.
3. To assess pre operative risk
4. To assess prognosis.

5. To assess health status before beginning strenuous physical activity programme.

Monitoring:

1. To assess therapeutic interventions.
2. To describe the course of disease that affect lung function
3. To monitor people exposed to injurious agents.

Disability/ impairment evaluation:

1. To assesspatients as a part of rehabilitation programme.
2. To assess risk as a part of insurance evaluation.
3. To assess individuals for legal reasons.

Public health:

1. epidemiological surveys
2. Clinical research.

Contraindications of pulmonary function test:

1. History of myocardial infarction within one month.
2. Unstable angina.
3. Recent thoraco abdominal surgeries.
4. Recent ophthalmic surgery.
5. Thoracic or abdominal aneurysm.
6. Current pneumothorax.

7. Acutely ill patients and in patients with active infection PFT should be deferred [141].

Factors affecting PFT:

Pulmonary function test is influenced by various factors like age, sex, height, weight, body position, ethnicity, technical variations, socioeconomic status, genetic and environmental factors.

Medications and hot beverages prior to test have a direct influence on the outcome of the test. Errors do occur with instrument, procedures, control values and calculations and standardisation minimises this type of errors. Calibration is the adjustment of the machine output and its validity reflects a known input.

Physiological determinants of PFT include age, height, sex, ethnicity and body position [142].

Age:

Lung development occurs during the first two decades of life and matures by 20- 25 years and lung functions become steady later on. As age progresses, the lungs undergo structural, functional and immunological changes [143].

Estenne et al found out that decrease in compliance of chest wall and diaphragm- abdomen compartment with increasing age in 61 healthy adults aged between 24- 75 years. Respiratory muscle strength can be assessed by measuring maximal voluntary ventilation, maximum inspiratory pressure and trans diaphragmatic pressure [144].

Enright and co workers showed the decrease in maximum inspiratory pressure in elderly people aged between 65- 85 years and this decrease was more in men[145]. Tolep et al showed decline in respiratory muscle strength with advancing age [146].

Mc Claran and co- workers, demonstrated that there was a decline in maximum voluntary ventilation in elderly individuals [147].

Changes in lung parenchyma and peripheral airways with age were studied in senescence accelerated mice. Teramoto et al [148] and kurozumi et al [149] conducted two different studies and found out in senescence accelerated mice that enlargement of alveolar duct size was seen with advancing age. Distension of alveolar spaces and increase in lung volumes were explained by decrease in elastic fibres of lung resulting in distension of alveolar spaces.

Verbeken et al by morphometric technique studied excised human lung after autopsy which showed increased thickening of alveolar septa and isolated airspace enlargement but there was no destruction of alveolar walls or signs of inflammation [150].

Gillooly and Lamb also found out increased airspace size in autopsy specimens[151]. Niewoehner et al by autopsy studies assessed the mean bronchiolar diameter and found that the diameter decreased after age of 40. This finding along with decrease in supporting tissues around the airways may contribute to decline in expiratory flow noted with aging[152].

Increased residual volume of about 50% is seen between 20- 70 years. This may be due to loss of elastic recoil of lung parenchyma and decrease in respiratory muscle strength. Increased stiffness of chest wall results in progressive decrease in vital capacity.

Total lung capacity remains almost constant throughout life. Functional Residual Capacity increases as age advances because of increased elastic recoil of chest wall and decreased elastic recoil of lung parenchyma.

Forced Expiratory Volume increase with age group upto 18 years and then starts to decline. FEV_1 and FVC show no change between 18- 25 years of age and then start to decline [153]. Some studies prove that this decrease in these parameters was found to be linear [154- 156].

According to Dockery et al and burrows et al, decrease in these parameters was non- linear. Decline in FEV_1 starting from 35- 40 years is 25- 30 ml/ year and rate of decline doubles after 70 years of age [157]. A study by Schimdt and colleagues showed that FEV_1/ FVC values remain stable in young adults. FEV_1/ FVC values decrease in females above 55 years and in males above 60 years [158].

Fowler et al studied 136 subjects above 60 years and found out decrease in Peak Expiratory Flow Rate which is due to loss of elastic recoil of lung, changes in peripheral airways and due to loss of supporting tissue around the airways [159].

Height:

ATS recommends that height measurement of subject undergoing PFT should be done with stadiometer using standard technique. Lung volumes are dependent on the body size and height of the individual such

that same height males have larger lung function values when compared to females and Whites have greater values compared to Blacks.

It was Hutchinson who first correlated vital capacity with standing body height. Kelly in 1993 found out the relationship between vital capacity and with third power of height. In 1950 Bateman found out relation of cube of height of adults with average status with total lung capacity and its sub divisions [160].

During growth spurt standing height increases and lung growth lags behind. So there occurs a change in relationship between these two during adolescence.

Weight:

Shoenberg et al in 1978 and Chen et al in 1993 studied flow volume curves of 7123 men and studied their relation with age, weight and standing height. They noticed an initial increase in lung function with increasing weight and it was explained to be due to increase in muscle force. But as weight increased further lung function decreased. This was due to limitation of mobility of thoracic cage due to obesity [161,162].

Bande et al in 1980 found out a decline in FVC and FEV_1 with weight gain[163]. Dontas studied FVC and $FEV_{75\%}$ of 592 men aged 25- 74

years in 1960, 1965 and in 1970 and found increase in body weight intensified the age dependent loss of FVC and $FEV_{75\%}$ [164].

Nemery in 1983 conducted a cross sectional study in steel workers aged 45- 55 years. Study included both smokers and non- smokers. The study showed significant positive correlation in smokers only [165]. Ray studied the effect of obesity on respiratory function in 43 massive obese, non smoking young adults. This study showed no significant relation [166].

Thomas in 1989 studied 29 morbidly obese subjects before and after weight reduction surgery. Loss of weight in these subjects was associated with improvement in lung function[167]. Chen found out that weight gain was more prominent predictor of decline in pulmonary function.

In men significant relations were observed in FVC, FEV_1 and $FEF_{25-75\%}$ and in females relations were observed in FVC and FEV_1. It was found that 1 kg increase in weight was associated with an excess loss of 26 ml in FVC in males and 14 ml in females. In FEV_1 a drop of 23 ml was seen in men and 9 ml in females [162].

Gender:

Lung volumes and capacities of males and females of same age, height and weight are different. Mead and Thurlbeck revealed larger diameter airways, larger lung volumes and larger diffusion surfaces in males.

In females, fewer number of alveoli and smaller airway diameter relative to lung size result in lower diffusion capacity[168,169]. There was no sex difference in the elastic properties of lung, chest wall and compliance[170].

Ethnicity:

Many studies prove differences in lung function values but the reason for these variations were not clearly understood. In 1983 His studied 1800 normal children of Black, White and Mexico American ethnic groups of age between 7- 20 years. They found out that using sitting height as predictor decreased racial difference among the study groups [171]. In 1984 Myers considered role of social class status on ethnic variation of lung function in South African Blacks. Their lung function values were compared with their normal predicted values and found out that predicted values suggested for them were higher [172]. He explained

this disparity in terms of confounding effect of social status. Donelly et al studied Caucasians, Chinese and Indians and found out that TLC, FVC and FEV_1. TLC was 15- 22% lower in Indians and Chinese when compared with that of Caucasians. Shape of chest wall appeared to be an important determinant of TLC. Caucasians have wider chest wall. They suggested that difference in lung volumes were not due to alveolar distension or inspiratory muscle pressure but due to difference in number of alveoli which in turn depends on chest shape [173].

In 2001 Hrik khan suggested roles of racial differences in upper and lower body segments ratio and socio economic status [174]. Whittaker and et al tested the hypothesis that ethical variations were due to difference in chest size. They found out that height was a predictor of lung function, but taking sitting height instead of standing height does not show any difference. Chest size was a predictor for FVC and FEV_1 and chest height was the best predictor of PEFR. $FEF_{25-75\%}$ does not depend on chest dimensions [175].

Body Position:

While performing PFT patient can adopt sitting standing position. But sitting posture was preferred during the manoeuvre because of safety

reasons as some procedures can cause fall due to syncope. In normal weight individuals the sitting and standing values are typically equivalent.

But in obese individuals, standing posture is preferred. They can make deep inspiration in standing position. Change from standing to the supine position decrease VC, FRC and TLC. This can be explained by upward shift of diaphragm, change in chest wall dimension and increase in thoracic blood volume [176].

AIM AND OBJECTIVES

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AIM

To evaluate the changes in dynamic respiratory functions of spray painters.

OBJECTIVES

1. To measure dynamic respiratory functions in spray painters using Easyone Diagnostic Spirometer.

2. To measure serum of immunoglobulin E (IgE) level

3. To calculate absolute eosinophil count.

4. To compare parameters of study group with that of control group.

MATERIALS AND METHOD

MATERIALS AND METHODS

Sample size:

30

Study design:

Cross sectional study

Study population:

Spray painters of age group 25 to 50 years.

Study duration:

From July – October 2014.

Ethical considerations:

Institutional ethical committee approval was obtained.

Parameters compared:

1. In PFT,
    I. Forced Vital Capacity (FVC) in (lit)
    II. Forced Expiratory Volume in 1st second (FEV_1) as (%)

III. FEV_1/FVC

IV. Mean Forced Expiratory Flow ($FEF_{25-75\%}$) as (lit/sec)

V. Peak Expiratory Flow Rate (PEFR) as (lit/min) and

VI. Maximum Voluntary Ventilation (MVV) as (lit/min).

2. Level of IgE and

3. Absolute eosinophil count.

Inclusion criteria:

1. Spray painters of age group 25- 50 years, who are involved in spray painting for duration more than 2 years.

2. Controls not exposed to spray painting of age group 25- 50 years from Master health check- up clinic at Stanley Medical College.

Exclusion criteria:

1. Asthmatics
2. History suggestive of worm infestations
3. Chronic allergic manifestations
4. Tuberculosis
5. Systemic illness like diabetes, hypertension
6. Renal and hepatic insufficiency
7. Smokers

8. Alcoholics
9. Other lung diseases.

Pre- requisites:

- The subjects were instructed to have light breakfast.
- The subjects were instructed to avoid beverages before recording PFT.
- The subjects were made to get accustomed to research laboratory.
- The research room was made calm and comfortable to the subjects.
- The procedure was explained in their own language.
- The explanation and demonstration of the procedure was done.
- The subjects were properly instructed and motivated.

Methodology:

After obtaining informed written consent from the subjects in their own language, pulmonary function test was recorded in research lab, Department of Physiology, Stanley Medical College using Easyone diagnostic spirometer. Pre-structured proforma based on Occupational Safety and Health Adminstration (OSHA) Respirator Medical Evaluation

Questionnaire containing name, age, gender, height in cms, weight in kgs and duration of exposure of the subjects, medical history and occupational history was recorded.

The entire procedure was explained and later demonstrated to the subjects satisfactorily before recording PFT, as spirometry test requires active participation by the subjects. PFT was recorded in the upright sitting posture in the morning using the Easy one Diagnostic Spirometer.

Forced Vital Capacity (FVC):

After choosing PERFORM TEST in the main menu we should choose NEW and confirm by pressing ENTER. The instrument will then allow us to enter the study subject's data. After entering the patient data, we move on to the TEST SELECTION menu. Then we choose the FVC test and confirm with ENTER. A spirette is inserted into the instrument such that the arrow on the spirette is lined up with the arrow on the instrument. When the patient is ready, we should press ENTER so that we hear the sensor buzzing. Now the instrument sets baseline and during this phase we have to avoid air flow into the spirette. Blocking one end of the spirette ensures that the baseline is set precisely. When the baseline has been set, an audible signal will sound followed by BLAST OUT on the display. Now the subject is asked to breathe in deeply and the spirette is

inserted correctly into the mouth such that no air leaks out. Now the subject is asked to exhale as firmly and as quickly as possible, and continue exhaling until all air has been exhaled and then followed by a deep maximum inhalation. At least three acceptable and reproducible maneuvers should be performed and the session is complete when the display shows SESSION COMPLETE[177].

Other parameters Forced Expiratory Volume in 1st second (FEV_1), FEV_1/ FVC ratio, Mean Forced Expiratory Flow ($FEF_{25-75\%}$) and Peak Expiratory Flow Rate (PEFR) was calculated and data is provided by the Easyone diagnostic spirometer.

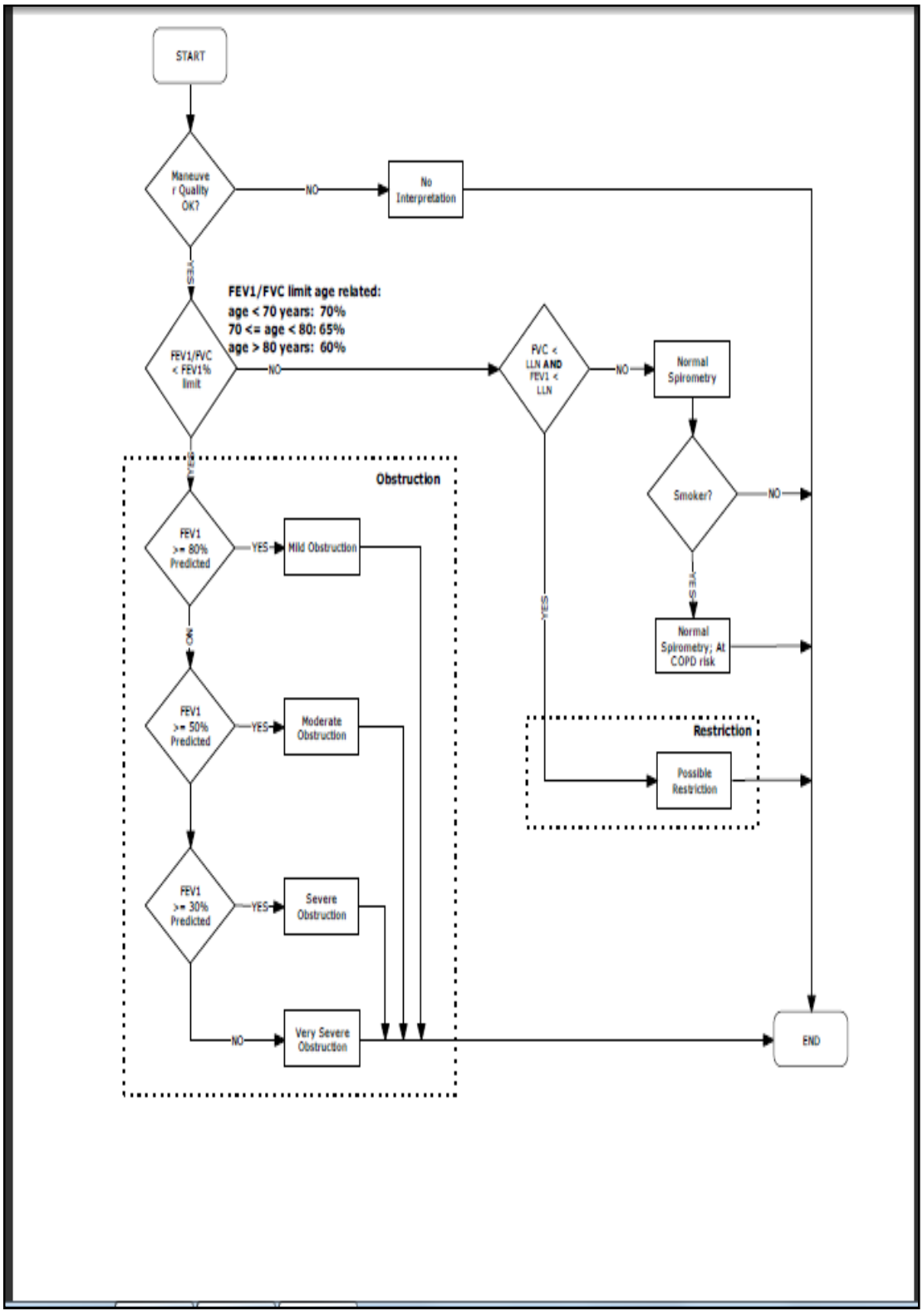
Maximum Voluntary Ventilation (MVV):

After meeting all above said pre requisites, the subject inserts the spirette into their mouth and fully inhales and exhales for an uninterrupted period of at least 12 seconds. This measures the maximum voluntary ventilation.

Interpretation of pulmonary function test parameters was done based on GOLD/ Hardie interpretation.

After recording PFT, blood sample was collected from the subjects under strict sterile aseptic precautions. Using disposable syringes 5 ml of blood was removed which was immediately replaced into red tube for IgE measurement and lavender tube with EDTA for Absolute Eosinophil Count which was sent to Dr.Ganesan's Hitech Diagnostic Centre PVT Ltd, Chennai for laboratory procedure. Picture 7, 8 & 9.

PICTURE – 7 : GOLD/HARDIE INTERPRETATION OF PFT.



PICTURE – 9 : REPORT OF PFT

STANLEY MEDICAL COLLEGE
CHENNAI 01

EasyOne(TM) DIAGNOSTIC EU 6.7
(c)ndd 2000-2011
EasyWare 2.24.0.0 - 09.09.2014 19:18
SN 104923 RecNo 444

Patient Information

Name	B POLARAJ
ID	0516
Age	37 (20.05.1977)
Height	161 cm
Weight	80 kg,BMI 30.9
Gender	MALE
Ethnic	ASIAN
Smoker	NO
Asthma	NO

Test Information

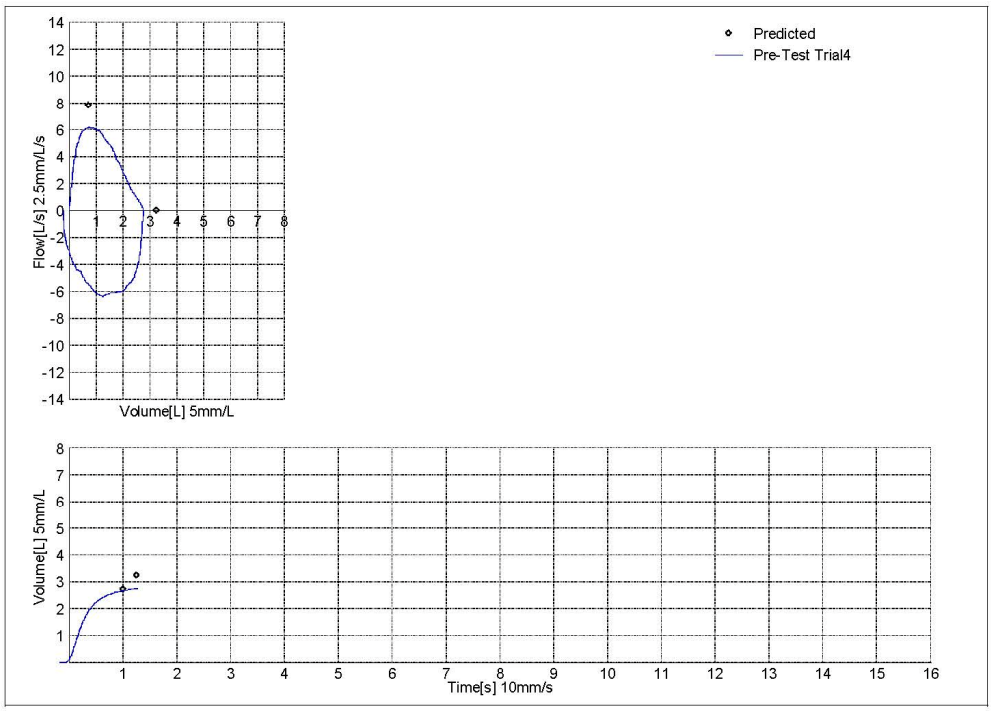
Test Date/Time	11.07.2014 12:28
Post Time	--:--
Test Mode	DIAGNOSTIC
Syst. Interpret.	GOLD/Hardie
Predicted Ref	Knudson 83 * 0.88
Value Select	BEST VALUE
Tech ID	
Automated QC	ON
BTPS (IN/EX)	1.07/ 1.02

FVC Test Results **Your FEV1 is 98% Predicted**

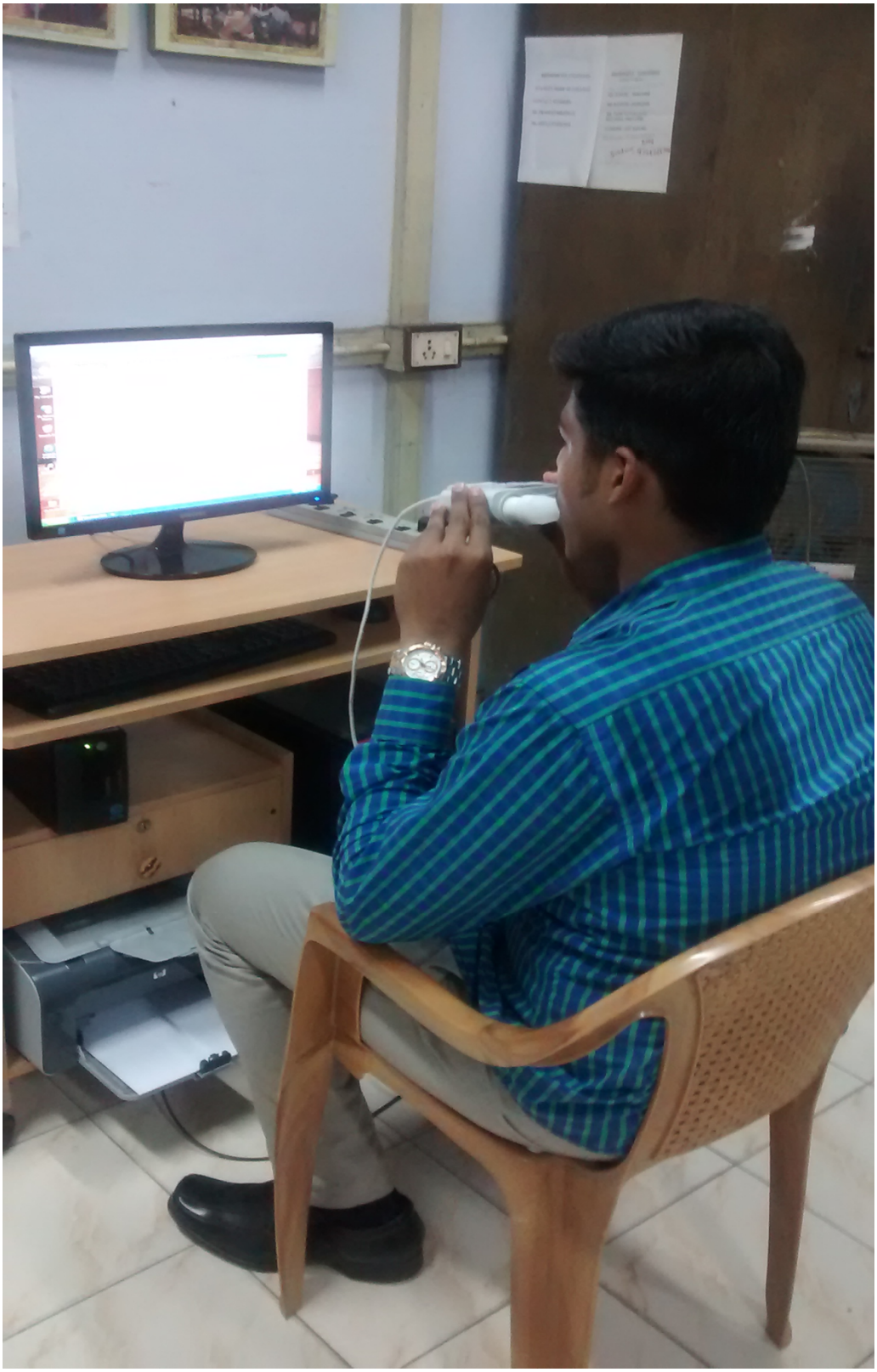
Parameter	Best	Pred	%Pred
FVC[L]	2.75	3.26	84
FEV1[L]	2.68	2.74	98
FEV1/FVC[%]	97.5	82.8	118
PEF[L/s]	6.16*	7.85	79
MEF25-75[L/s]	4.58	3.46	132
MEF75[L/s]	6.13	-.--	--
MEF50[L/s]	5.20	4.12	126
MEF25[L/s]	2.62	1.66	158
FIVC[L]	2.98	3.26	92
PIF[L/s]	6.37	-.--	--

*** Indicates Below LLN**

Pre-Test FEV1 Var=0.07L 2.6%;FVC Var=0.04L 1.3%;Session Quality C
Syst. Interpret. Normal Spirometry



PICTURE – 8 : RECORDING OF PFT - NEURO PHYSIOLOGY LAB PHYSIOLOGY DEPARTMENT, STANLEY MEDICAL COLLEGE



STATISTICAL ANALYSIS

Data collected was stored and analyzed statistically by unpaired student t test using SPSS version 17.0. The Data is expressed as mean ± standard deviation. Statistical significance was tested using p value.

p value < 0.050- Significant.

p value < 0.010 - Highly significant.

RESULTS

RESULTS

In this present study, pulmonary function test was recorded in 30 individuals exposed to spray painting and the parameters studied were FVC, FEV_1, FEV_1/ FVC, $FEF_{25-75\%}$, PEFR and MVV. Along with this, measurement of IgE and Absolute Eosinophil Count (AEC) was done and compared with that of age matched 30 individuals not exposed to spray painting.

The data are expressed as Mean ± Standard deviation and p value < 0.05 is taken as significant.

The baseline characteristics of the study group and control group are shown in table 4. Of the total 30 subjects in study group, the mean age in years is 45 ± 4, mean height in centimetres is 158 ± 8, mean weight in kilograms is 73 ± 12 and mean BMI is 29 ± 4 and that of 30 subjects in control group the mean age in years is 44 ± 4, mean height in centimetres is 159 ± 6, mean weight in kilograms is 71 ± 10 and mean BMI is 28 ± 4.

From table 5, it is observed that there is a highly significant change in FVC (2.40 ± 0.31), FEV_1 (2.16 ± 0.26) and significant change in FEV_1/ FVC (0.90 ± 0.08) among study group when compared to that of control

group FVC (3.29 ± 0.27), FEV_1 (3.11 ± 0.28) and FEV_1/ FVC (0.95 ± 0.04).

From table 6, it is observed that there is a highly significant change in PEF (4.80 ± 1.74) and $MEF_{25-75\%}$ (3.01 ± 1.07) among study group when compared to that of control group PEF (6.46 ± 1.91) and $MEF_{25-75\%}$ (4.47 ± 0.82).

From table 7, it is observed that there is a highly significant change in MVV (82.35 ± 20.07) among study group when compared to that of control group MVV (102.56 ± 25.15).

From table 8, it is observed that IgE (410 ± 20) and AEC (333 ± 22) are significantly increased in study group when compared to that of control group IgE (97 ± 41) and AEC (228 ± 90).

In table 9, duration of exposure to spray painting and pulmonary function test has been correlated and found that there is a significant correlation existed between $MEF_{25-75\%}$ and duration of exposure. No significant correlation demonstrated between FVC, FEV_1, FEV_1/ FVC, PEF and MVV and duration of spray paint exposure.

In table 10, duration to exposure to spray painting and IgE levels and AEC was correlated and found that there was no significant correlation between the two parameters.

While correlating IgE levels and parameters of pulmonary function test in table 11, we found that the correlation was not significant.

While correlating AEC and parameters of pulmonary function test in table 12, we found that the correlation was not significant.

TABLES AND CHARTS

Table 4: Comparison of basic parameters of control and study group:

Parameters studied	Control group n= 30 Mean ± SD	Study group n= 30 Mean ± SD	p value
Age (years)	44 ± 4	45 ± 4	0.152
Height (cms)	159 ± 6	158 ± 8	0.410
Weight (kgs)	71 ± 10	73 ± 12	0.608
BMI	28 ± 4	29 ± 4	0.303

**p value ≤ 0.001 is highly significant

*p value ≤ 0.05 is significant

Chart 1: Comparison of basic parameters of control and study group:

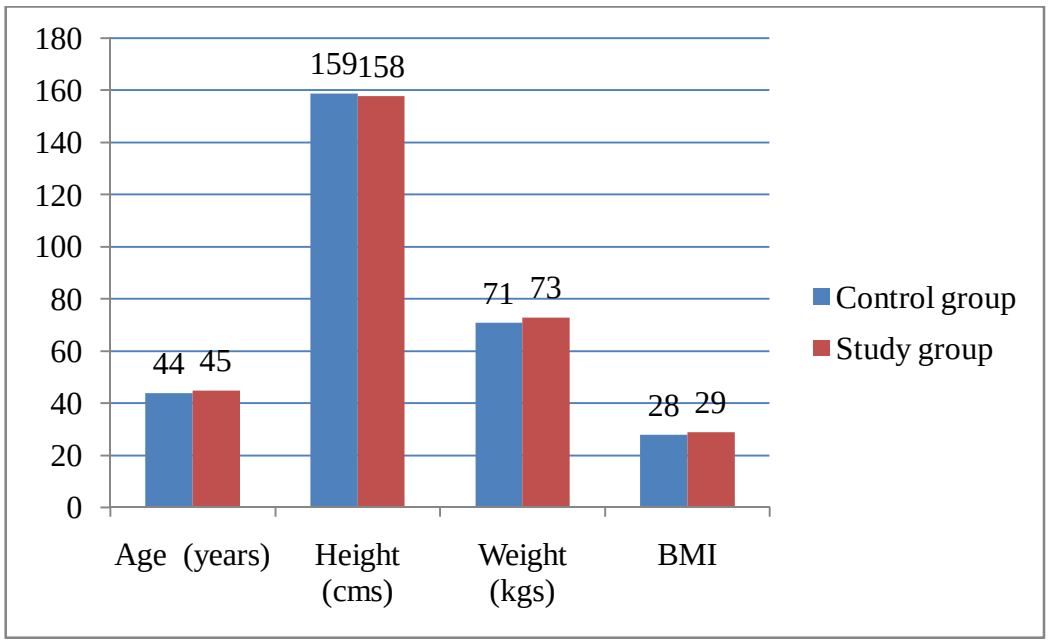


Table 5: Comparison of FVC, FEV_1 and FEV_1/ FVC among control and study group:

Parameters studied	Control group n= 30 Mean ± SD	Study group n= 30 Mean ± SD	p value
FVC(L)	3.29 ± 0.27	2.40 ± 0.31	0.001**
FEV_1(L)	3.11 ± 0.28	2.16 ± 0.26	0.001**
FEV_1/ FVC	0.95 ± 0.04	0.90 ± 0.08	0.011*

**p value ≤ 0.001 is highly significant

*p value ≤ 0.05 is significant

Chart 2: Comparison of FVC, FEV_1 and FEV_1/ FVC among control and study group:

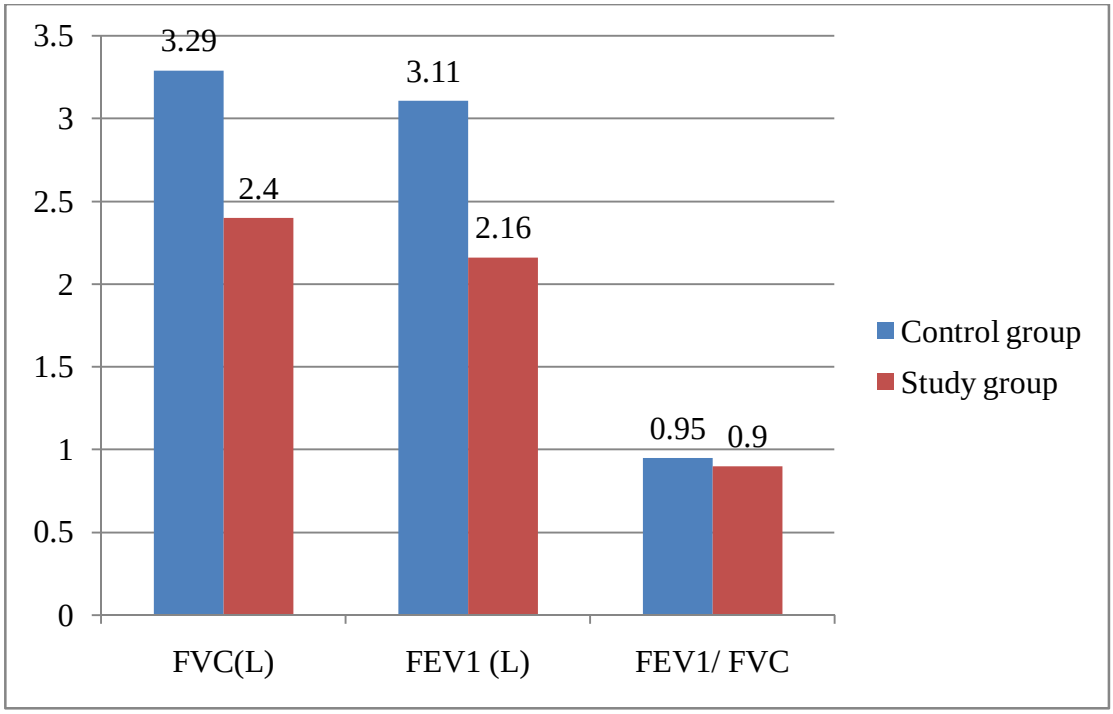


Table 6: Comparison of PEF and $MEF_{25-75\%}$, among control and study group:

Parameters studied	Control group n= 30 Mean ± SD	Study Group n= 30 Mean ± SD	p value
PEF(L/S)	6.46 ± 1.91	4.80 ± 1.74	0.001**
$MEF_{25-75\%}$(L/S)	4.47 ± 0.82	3.01 ± 1.07	0.001**

** p value ≤ 0.001 is highly significant

*p value ≤ 0.05 is significant

Chart 3: Comparison of PEF and $MEF_{25-75\%}$ among control and study group:

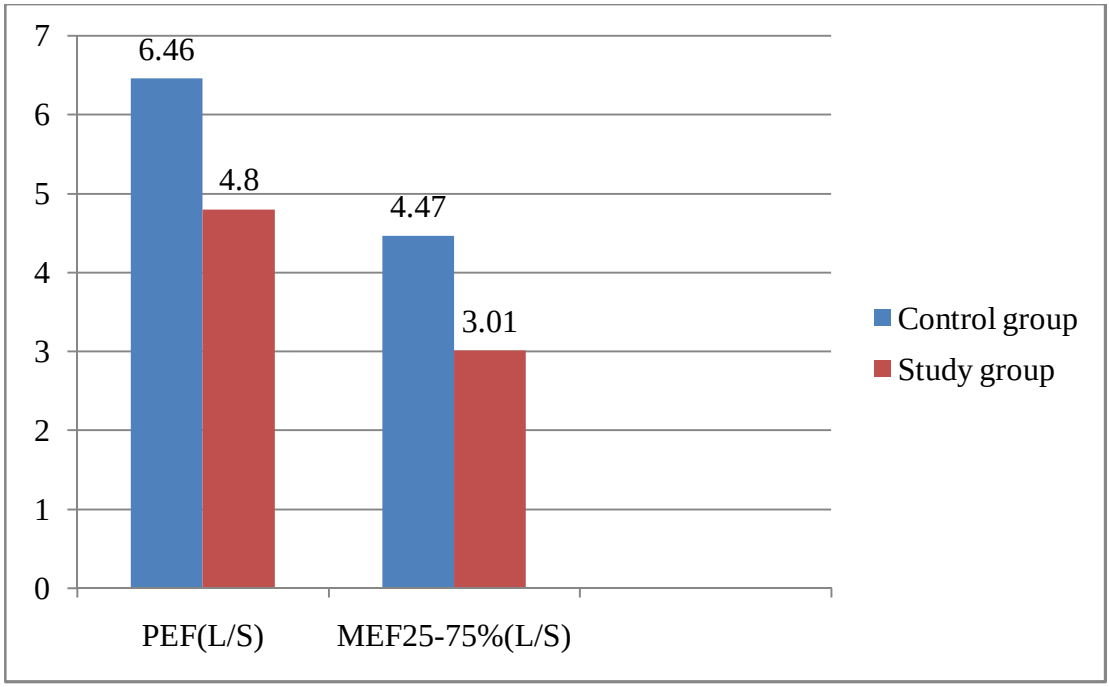


Table 7: Comparison of MVV among control and study group:

Parameters studied	Control group n= 30 Mean ± SD	Study Group n= 30 Mean ± SD	p value
MVV(L/M)	102.56 ± 25.15	82.35 ± 20.07	0.001**

**p value ≤ 0.001 is highly significant

*p value ≤ 0.05 is significant

Chart 4: Comparison of MVV among control and study group:

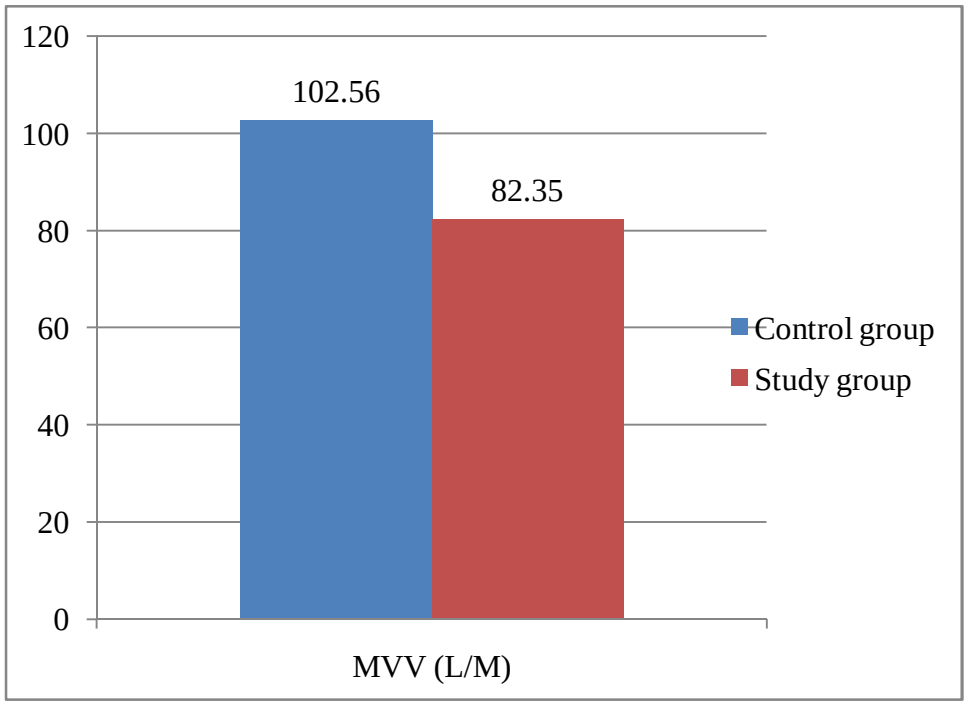


Table 8: Comparison of IgE and AEC among control and study group:

Parameters studied	Control group n= 30 Mean ± SD	Study Group n= 30 Mean ± SD	p value
IgE(IU/ML)	97 ± 41	410 ± 20	0.001**
AEC(Cells/Cmm)	228 ± 90	333 ± 22	0.017*

**p value ≤ 0.001 is highly significant

*p value ≤ 0.05 is significant

Chart 5: Comparison of IgE and AEC among control and study group:

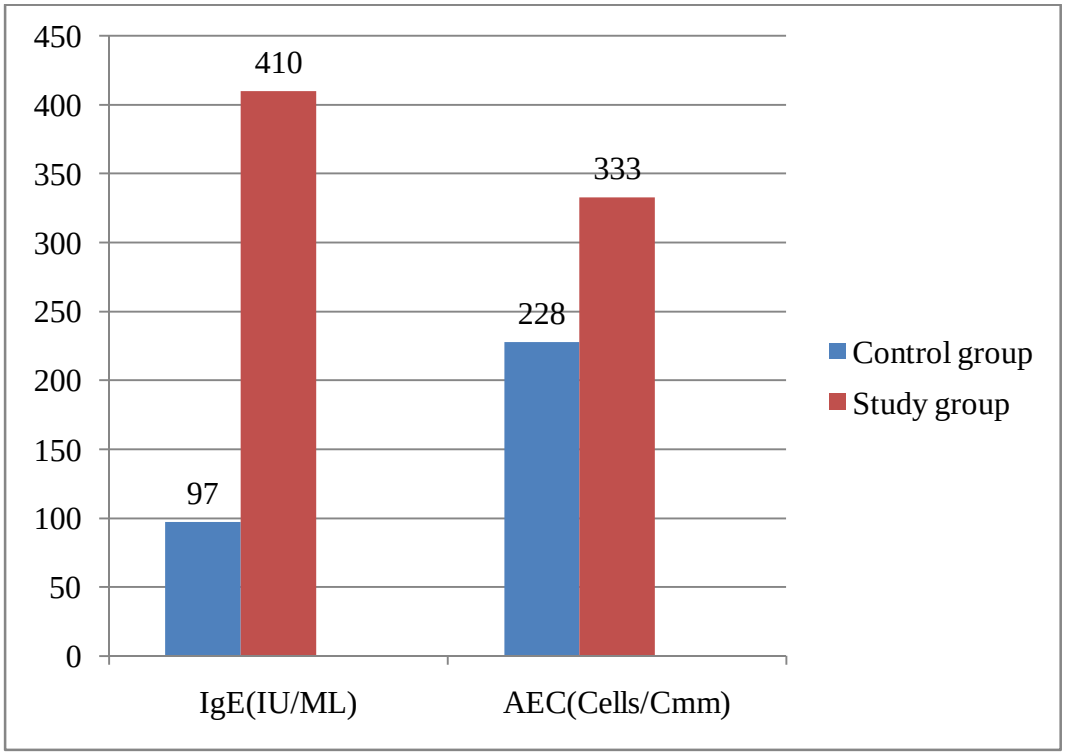


Table 9: Correlation between duration of spray paint exposure and pulmonary function test parameters in study group:

Duration of spray paint exposure	Parameters studied						
	Pearson Correlation	**FVC**	**FEV_1**	**FEV_1/ FVC**	**PEF**	**$MEF_{25-75\%}$**	**MVV**
	r Value	-0.08	-0.29	-0.25	-0.19	-0.42*	-0.16
	p value	0.67	0.12	0.18	0.31	0.02*	0.39

* p value $\leq$ 0.05 is significant.

Significant p value- 0.02*

Statistically significant correlation existed between $MEF_{25-75\%}$ and duration of exposure.

No statistically significant correlation demonstrated between FVC, FEV_1, FEV_1/ FVC, PEF and MVV and duration of spray paint exposure.

Table 10: Correlation between duration of spray paint exposure and IgE level and AEC in study group:

Duration of spray paint exposure	Pearson Correlation	IgE	AEC
	r Value	-0.26	-0.26
	P value	0.16	0.16

* p value ≤ 0.05 is significant.

No statistically significant correlation between duration of spray paint exposure and IgE levels and AEC.

Table 11: Correlation between IgE and pulmonary function test parameters in study group:

	Parameters studied						
	Pearson Correlation	**FVC**	**FEV_1**	**FEV_1/ FVC**	**PEF**	**MEF 25-75%**	**MVV**
IgE	r Value	-0.04	-0.30	-0.29	-0.31	-0.27	0.01
	p value	0.84	0.11	0.11	0.10	0.15	0.98

* p value ≤ 0.05 is significant.

No statistically significant correlation between IgE levels and pulmonary function test parameters.

Table 12: Correlation between AEC and pulmonary function test parameters in study group:

AEC	Parameters studied						
	Pearson Correlation	**FVC**	**FEV_1**	**FEV_1/ FVC**	**PEF**	**MEF 25-75%**	**MVV**
	r Value	0.01	0.01	-0.04	-0.05	-0.10	-0.25
	P value	0.94	0.97	0.829	0.78	0.60	0.18

* p value ≤ 0.05 is significant.

No statistically significant correlation between AEC and pulmonary function test parameters.

DISCUSSION

DISCUSSION

Measurement of pulmonary function tests in individuals exposed to spray painting has proven to be an important diagnostic tool. Di-isocyanates are among the most common causes of occupational asthma[3]. Di-isocyanates cause asthma by inducing intense airway inflammation and cause a major health effect. It also causes accelerated decline in lung function[6].

Overall 5 to 30 percent of workers exposed to toluene di-isocyanate develop airway symptoms. One study which examined the decremental fall in flow rates in workers exposed to toluene di-isocyanate predicted a 2 Litre greater loss in FEV_1 in these workers when compared with controls [90].

Musk et al reviewed the known respiratory effects of isocyanates and showed good evidence that isocyanates can cause chemical bronchitis/ pneumonitis and capabale of causing isocyanate asthma and other non specific airway disease [109].

In this study we compared the respiratory function test parameters of study and control group. The respiratory parameters compared were FVC, FEV_1, FEV_1/ FVC, PEFR, $FEF_{25-75\%}$ and MVV. Along with this we

also compared the IgE levels and AEC among the study and control group.

On comparing the demographic profile of these individuals, age matched, BMI matched individuals were included in this study. The mean age was 45 years with standard deviation ranging from 41 to 49 years in study group and the mean age was 44 years with standard deviation ranging from 40 to 48 years in control group. According to a study conducted by Gupta et al, he suggested that there was a significant age related senile asthma occurring after 50 years in Indian population [178]. Hence in our study we excluded spray painters who are more than 50 years in order to rule out bias due to age related respiratory changes.

The mean height was 158 cms with standard deviation ranging from 150 to 166 cms in study group and the mean height was 159 cms with standard deviation ranging from 153 to 165 cms in control group showing not a much difference, because vital capacity has a correlation with regard to height as studied by Bateman et al[160].

The mean weight was 73 kilograms with standard deviation ranging from 61 to 85 kilograms in study group and the mean weight was 71 kilograms with standard deviation ranging from 61 to 81 kilograms in control group with not a much difference among study and control group

since increased weight and obesity has a direct effect on lung function due to decreased mobility of thoracic cage as stated by Shoenberg et al[161].

FVC, FEV_1 and FEV_1/ FVC are better indicators to differentiate obstructive or restrictive lung disease. Isocyanate exposure in spray paint produce occupational asthma which causes an obstructive type of lung disease substantiated by normal or decrease in FVC, decrease in FEV_1 and decrease in FEV_1/ FVC ratio.

Pronk et al, found a strong positive association between isocyante exposure and bronchial hyperresponse which is detected by significant change in FEV_1/ FVC ratio. In our study too we found that there is significant decrease in FVC, FEV_1 and FEV_1/ FVC ratio concurring with the findings of Pronk et al and Wegman et al[96,109]. This significant decrease in lung parameters was due to isocyanate induce chemical bronchitis which serve as a potent pulmonary sensitizer causing non specific airway disease and asthma.

Siddanagoudra et al while studying respiratory morbidity in spray paint workers in an automobile sector, found that, of the 70 car paint workers included in this study, nine isocyanate-exposed workers showed a significant reduction in FEV_1/ FVC suggestive of obstructive lung

pattern and a strong correlation between duration of exposure and pulmonary functions [179].

Peak expiratory flow rate is a better indicator of larger central airway disease, and helps to assess the severity of an asthma attack and to assess the response to treatment during an acute attack.

In our study we found that there is a significant decline in PEFR in study group when compared to control group indicating a larger airway involvement due to spray paint. Randolph et al studied PEFR in 21 subjects and did serial measurements of PEFR for 30 days and he concluded that PEFR is an insufficient sensitive indicator [82].

Burge et al concurs with these results showing that PEFR are proportionally less than FEV in the same individual and concluded that linear calibration of peak flow meters is needed[80].

$FEF_{25-75\%}$ is a better indicator of smaller airway disease. Randolph et al, concluded that even though FEV_1 helps to predict OA, he has suggested that $FEF_{25-75\%}$ seems to be a better predictor of small airway disease. In our study too we found that there is a statistically significant change in $FEF_{25-75\%}$ concurring with Randolph et al[82].

While correlating duration of spray paint exposure and respiratory compromise in our study, there was a strong negative correlation between $FEF_{25-75\%}$ indicating smaller airway involvement as duration increases concurring with Mandal et al where he found a strong negative correlation between pulmonary functions and duration of exposure to solvents and dust[104].

Chattopadhyay et al in his 2.5 years follow-up study observed that pulmonary function parameters of isocyanate exposed workers for long duration were reduced even in very low concentration [98] concurring with findings of Mandal et al[104].

MVV is more a sensitive indicator of airflow obstruction and in our study too shows a significant decrease in MVV when compared to control group emphasising the fact that obstructive airway disease is seen in isocyanate induced asthma.

IgE levels were significantly elevated in our study group exposed to spray painting in agreement with Pezzini et al were he found that a specific IgE-mediated response in twenty-eight workers exposed to toluene di-isocyanate or diphenyl-methane di-isocyanate. The results suggest an association between the presence of specific IgE, early asthmatic symptoms and heavy episodic exposure[107].

AEC is significantly elevated in study group showing a strong relationship between isocyante exposure and allergic reactions concurring with Jagadeeshwar et al[125] and Agha et al[111].

Correlation between duration of exposure to spray paint and IgE level and AEC in study group showed weak negative correlation, which was not significant statistically. This is due to the reason that the individual gets conditioned to the allergic aspect as the duration of spray paint exposure prolongs. This concurred with Tee et al, where in his study he reported that specific IgE to isocyanate was higher when blood was taken less than 30 days after last exposure[114].

Correlation between IgE and AEC and pulmonary function test parameters in study group showed weak negative correlation but not statistically significant. This outcome of the study concurred with Chan et al where he found that, continuous exposure to isocyanate in sensitised individuals led to deterioration in lung function and increase in non-specific bronchial reactivity[68].

Thus from above studies, we observe that isocycrates in spray paint produce a marked respiratory compromise leading to occupational asthma. This can be detected by measuring pulmonary function test in individuals working with spray paint. Measuring IgE along with

pulmonary function test serves as a sensitive indicator if done early during the period of exposure.

Also measuring Absolute Eosinophil Count along with PFT and IgE serves as a strong evidence for allergic component involvement and bronchial hyperreactivity. Our study too supports the above finding and hence from our study we conclude that pulmonary function test done along with IgE and AEC measurement can be used as an early investigatory tool to bring down the morbidity.

SUMMARY

SUMMARY

Occupational health hazards and health problems lay unaware in developing nations when compared to developed countries.

Changes in pulmonary function test in workers in spray painting and measurement of IgE and AEC in them proves a strong association between development of bronchial hyperreactivity and asthma.

Periodic inspection of working environment provides information and helps in anticipation of occupational disabilities. Work place environment should be designed according to norms suggested so that is does not affect the health of workers.

The correct use of protective devices like masks and gloves should be explained. They should be frequently health educated using charts, posters and hand bills.

Periodical medical check-up of workers is very necessary when they handle toxic or poisonous substances.

Pre placement examination is the foundation of an efficient occupational health service. Pre placement examination will also serve as a useful bench mark for future comparison.

CONCLUSION

CONCLUSION

Thus on evaluating the changes in dynamic respiratory functions of spray painters, we conclude that there is a significant decrease in FVC, FEV_1, FEV_1/ FVC, PEFR, $MEF_{25-75\%}$ and MVV and significant increase in serum IgE levels and AEC in study group establishing a strong evidence for respiratory impairment due to isocyanates.

It is a fact that better investigatory tools for early recognition of occupational asthma can lead to early preventive strategies and provide means for improving the medical management of patients.

Prevention of isocyanate induced occupational asthma is the need of the hour and effective management is removal from the offending environment.

Prophylactic use of respirators in areas with high concentrations of isocyanates is essential to prevent the development of asthma.

The other protective devices comprise ear plugs, helmets, safety shoes, aprons, gloves, gum boots, barrier creams, screens and goggles.

In future pulmonary function test, IgE and AEC estimations may be a sensitive means to correlate isocyanate exposure and respiratory disease.

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ANNEXURES

ANNEXURE – I

PROFORMA

1. Serial Number:
2. Name:
3. Age:
4. Sex:
5. ID Number:
6. OP/IP Number:
   a. Personal history:
   b. Type of food habits: veg /non veg /mixed
   c. Type of house: kutcha /pucca /semi
   d. Religion: Hindu /Muslim /Christian /others
   e. Occupation: Duration:
   f. Per capita income: No. of family members:

      Net family income:
   g. Education qualification: nil education /class I-V /class VI-XII /college /professional
   h. Social habits: Smoking: active /passive

      Betel nut/leaf chewing: +/-
   i. Socio economic status: Skilled/ Semi skilled with fixed wages/ Semi skilled with daily wages
7. Martial history: Married/Unmarried
8. Clinical history:
   Height: Weight: Chest expansion:

Pulse rate: BP: Respiratory rate:

9. History suggestive of bronchial asthma: inhalers/ iv drugs/ constant nebulisation
10. History suggestive of tuberculosis:
11. History suggestive of worm infestations: abdominal discomfort/ altered bowel habits/
12. Investigations:

PFT:

IgE LEVEL:

ABSOLUTE ESINOPHIL COUNT:

ANNEXURE – II

CONSENT FORM

ஒப்புதல் படிவம்

திரு._____,
ஆகிய நான் டாக்டர்._____, பட்டமேற்படிப்பு மாணவி உடல் இயங்கியல் துறை, ஸ்டான்லி மருத்துவக் கல்லூரி, நடத்தும் நுரையீரல் செயற்கூறு பரிசோதனை, மற்றும் இரத்த பரிசோதனை செய்வதற்கு யாருடைய வற்புறுத்தலும் இன்றி என்னுடைய முழுசம்மதத்துடன் பங்கேற்க சம்மதம் தெரிவிக்கிறேன். இந்த ஆராய்ச்சியில் எந்தவித மருந்துகளோ ஊசிகளோ அளிக்கப்படவில்லை. நான் இந்த ஆராய்ச்சியில் இருந்து எந்தவித முன்னறிவிப்பும் இன்றி விலகிக்கொள்ள உரிமை உண்டு. இந்த ஆராய்ச்சியின் ஏடுகள் ரகசியமாக வைக்கப்படும் என்பதை நான் அறிவேன்.

கையொப்பம்

CONSENT FORM

I, Mr._____, agreed to participate in the study of pulmonary function test and blood investigations done by Dr._____, Post Graduate, Department of Physiology, Stanley Medical College, voluntarily. I have been informed that the study does not involve administration any drugs or injections. I can withdraw from the study /research at anytime without prior intimation and know that the results will be kept confidential.

SIGNATURE

ANNEXURE – III

INFORMATION FORM

தகவல் படிவம்

இந்த ஆய்வு, டாக்டர்._____, பட்டமேற்படிப்பு மாணவி உடல் இயங்கியல் துறை, ஸ்டான்லி மருத்துவக் கல்லூரி, அவர்களால் அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது. இதில் தொழிற்சாலையில் பயன்படுத்தப்படும் தெளி சாயம் (spray paint) ஏற்படுத்தும் பக்கவிளைவினை அறிய நுரையீரல் செயற்கூறு பரிசோதனை, மற்றும் இரத்த பரிசோதனை செய்யப்படுகிறது. நுரையீரல் மற்றும் இரத்ததில் வரும் மாற்றத்தை, வயது ஒத்த ஆண்களோடு ஒப்பிட்டு பார்க்கப்படுகிறது. இந்த ஆராய்ச்சியில் எந்தவித மருந்துகளோ ஊசிகளோ அளிக்கப்படவில்லை. இந்த ஆய்வில் சுய விருப்பத்துடன் பங்கேற்க முன் வந்தவர்கள் மட்டுமே ஆராய்ச்சியில் பங்கேற்க முடியும்.

MASTER SHEET

MASTER SHEET SHOWING OBSERVED VALUES

Id Controls	Age	Sex	Ht(cm)	Wt(kg)	BMI	Duration	FVC(L)	FEV_1 (L)	FEV_1/ FVC	PEF (L/s)	MEF_{25-75} (L/s)	MVV (L/m)	IgE (IU/ml)	AEC (cells/cmm)
505	45	m	160	60	23.4	-	3.38	3.19	0.95	7.31	4.96	130.6	94.6	210
508	49	m	156	75	30.8	-	3.05	2.89	0.88	5.11	3.72	124.7	64.5	250
525	45	m	162	65	24.8	-	3.19	3.01	0.94	5.52	4.09	107.6	84.1	300
526	38	m	168	80	28.3	-	3.31	2.88	0.84	3.66	3.01	70	67.5	170
527	46	m	161	70	27	-	3.31	2.91	0.81	4.02	3.67	65.7	104.1	300
529	47	m	161	66	25.5	-	3.46	3.08	0.89	7.53	3.84	81.4	143	100
531	46	m	159	62	24.5	-	3.29	3.17	0.96	4.53	4.11	99.6	31.73	120
533	46	m	159	75	29.7	-	3.34	3.05	0.91	8.52	4.77	115.3	106.8	170
534	42	m	168	75	26.6	-	3.11	3.04	0.98	8.52	5.76	144.8	128.6	280
535	46	m	161	74	28.5	-	3.19	2.95	0.85	8.34	3.85	88.5	134.5	270
538	40	m	153	76	32.5	-	3.32	3.19	0.93	5.29	4.37	81.7	166.5	460
539	45	m	162	71	27.1	-	3.16	3.15	1	4.94	3.95	78.5	143.8	250
540	50	m	167	74	26.5	-	3.11	3.01	0.97	8.3	5	87.2	58	160
541	45	m	150	68	30.2	-	3.11	3.04	0.98	8.52	5.76	144.8	97.2	260
542	39	m	154	67	28.3	-	3.02	2.99	0.99	6.65	5.04	91.5	35.9	180
543	38	m	165	92	33.8	-	3.48	3.23	0.93	4.24	3.95	114.4	58	260
544	47	m	157	65	26.4	-	3.98	3.64	0.91	8.83	5.53	143.1	110.5	350
546	38	m	168	75	26.6	-	3.16	3.15	1	4.94	3.95	78.5	126.5	110
547	47	m	145	47	22.4	-	3.17	3.17	1	4.97	3.94	88.5	85.2	200
548	47	m	172	86	29.1	-	3.11	2.87	0.92	6.25	4.32	104.9	36.2	120
549	38	m	161	86	33.2	-	3.98	3.64	0.91	8.83	5.53	143.1	27.37	260
550	38	m	162	79	30.1	-	3.48	3.47	1	9.48	5.99	126.5	68.7	130
551	47	m	162	67	25.5	-	3.16	2.81	0.89	4.02	3.23	116.3	126.5	110
552	40	m	164	66	24.5	-	3.11	3.01	0.97	8.3	5.17	88.2	171.6	180
557	38	m	152	66	28.6	-	3.04	2.91	0.96	3.78	3.47	77.3	47.99	220
558	48	m	156	71	29.2	-	3.11	3.01	0.97	8.5	5.11	97.2	106.8	420
559	43	m	157	51	20.7	-	3.18	3.17	1	5.63	4.67	85.8	142.8	260
560	47	m	149	90	40.5	-	3.16	3.15	1	4.94	3.95	78.5	121.7	170
561	48	m	155	74	30.8	-	3.98	3.64	0.91	8.83	5.53	143.1	140	330
562	47	m	157	65	26.4	-	3.22	2.85	0.88	5.57	3.88	79.6	76.8	240

Id Study Group	Age	Sex	Ht(cm)	Wt(kg)	BMI	Duration	FVC(L)	FEV_1 (L)	FEV_1/ FVC	PEF (L/s)	MEF_{25-75} (L/s)	MVV (L/m)	IgE (IU/ml)	AEC (cells/cmm)
501	49	m	180	73	22.5	7	2.96	2.09	0.71	2.63	1.85	103.3	524.12	290
502	50	m	160	85	33.2	7	2.37	2.07	0.87	4.58	2.52	67	539.6	220
506	45	m	159	82	32.4	12	2.15	2.11	0.98	6.55	4.14	83.1	305.61	540
507	49	m	156	65	26.7	10	2.47	2.4	0.97	6.43	3.34	79.8	199.63	600
509	50	m	144	40	19.3	8	1.81	1.8	0.99	5.26	2.92	70.8	660.91	140
510	50	m	147	65	30.1	12	2.32	2.03	0.87	5.02	2.7	80.5	318.14	600
511	49	m	155	62	25.8	12	2.1	1.83	0.87	4.08	2.14	84	2500	410
512	48	m	157	62	25.2	14	2.87	2.01	0.7	3.48	1.61	121	622.92	290
513	44	m	154	77	32.5	7	2.19	2.03	0.93	2.73	2.53	87	501.8	340
514	49	m	156	75	30.8	7	2.19	2.14	0.98	5.21	4.21	72.2	362.6	100
515	44	m	165	64	23.5	15	2.08	1.99	0.96	3.92	2.95	38.1	217.3	210
516	37	m	161	80	30.9	4	2.75	2.68	0.97	6.16	4.58	123.4	440.81	110
517	44	m	165	65	23.9	17	2.22	2.07	0.93	2.6	2.28	65.1	248.5	170
518	40	m	161	78	30.1	3	2.8	2.49	0.89	4.91	3.68	88.1	464.9	130
519	44	m	165	80	29.4	18	2.77	2.12	0.77	5.83	1.76	80.1	403.8	310
520	39	m	148	69	31.5	19	2.68	2.43	0.91	5.46	2.74	115	368.86	100
521	50	m	154	65	27.4	12	2.89	2.29	0.79	3.23	2.06	54.2	403.8	310
522	50	m	159	95	37.6	10	2.19	2.16	0.99	6.69	5.75	96.6	562.6	100
523	49	m	154	68	28.7	15	2.13	1.91	0.9	2.72	1.93	81.3	201.8	340
524	44	m	167	85	30.5	12	2.56	2.52	0.98	4.85	4.27	82	251.6	580
528	50	m	148	64	29.2	17	2.26	1.85	0.82	1.99	1.53	49.6	367.5	870
530	50	m	148	74	33.8	6	2.18	2.02	0.92	5.9	3.12	88.1	431.73	120
532	50	m	154	90	37.9	11	2.09	1.79	0.86	4.19	2.43	80.8	201.1	170
536	40	m	170	104	36	6	2.19	2.03	0.93	2.73	2.53	87	417.5	220
537	46	m	154	62	26.1	5	2.69	2.36	0.87	5.08	2.99	49	740.7	400
545	43	m	154	70	29.5	10	2.21	2.21	1	5.01	4.58	91.1	204	240
553	38	m	164	64	23.8	11	2.52	2.27	0.9	6.57	3.15	69.8	418.89	480
554	37	m	163	83	31.2	11	2.13	1.91	0.9	2.72	1.93	81.3	992.8	450
555	43	m	167	74	26.5	7	2.83	2.8	0.99	8.52	4.88	106.1	148.7	440
556	46	m	148	63	28.8	12	2.59	2.42	0.93	8.74	3.24	95.2	138.1	240